GENOMICS AND GLOBAL HEALTH

A Report of the Genomics Working Group of the Science and Technology Task Force of the United Nations Millennium Project

TABLE OF CONTENTS

CHAPTER 3

CHAPTER 4

FOREWORD

"Science has contributed immensely to human progress and to the development of modern society. The application of scientific knowledge continues to furnish powerful means for solving many of the challenges facing humanity, from food security to diseases such as AIDS, from pollution to the proliferation of weapons. Recent advances in information technology, genetics and biotechnology hold extraordinary prospects for individual well-being and humankind as a whole."

– Kofi Annan, United Nations Secretary-General
Science, March 7, 2003

The idea for this report was born out of conversations between the Task Force on Science and Technology of the United Nations Millennium Project (commissioned by the United Nations Secretary-General Kofi Annan) and researchers at the University of Toronto who had recently authored a study on the top 10 biotechnologies for improving health in developing countries. The result explores the relationships between genomics and the Millennium Development Goals (MDGs) and shows how cutting-edge science closely aligns with the UN's development agenda. It tackles aspects of both science and policy in the application of genomics towards the MDGs, and proposes a framework for collective action to promote genomics worldwide. Together with UNDP's 2001 *Human Development Report* on Making New Technologies Work for Human Development and WHO's 2002 report on Genomics and Global Health, it is an important benchmark to illustrate the potential of science and technology to close the development gap between Northern and Southern countries.

The MDGs emerged at the UN Millennium Summit in September 2000 as a set of clear targets for developing countries to achieve by 2015. They aim to reduce extreme poverty and hunger, achieve universal primary education and gender equity, reduce under-five mortality and maternal mortality, reverse the spread of HIV/AIDS, improve access to safe drinking water and ensure environmental sustainability. The eighth MDG aims to develop a global partnership for development, with targets for aid, trade and debt relief. The long-term vision of the MDGs is to create global learning mechanisms that can help build capacity in developing countries.

The ten task forces set up by the Millennium Project are currently conducting background research and devising a set of recommendations towards an implementation strategy to help developing countries meet the MDGs. These task forces are oriented around areas such as poverty, hunger, primary education, and science and technology. The mission of the Science and Technology Task Force is guided by the belief that science is a necessary cog in the wheel of development. It is not difficult to argue that science, technology and innovation underpin every MDG – maternal and child mortality, hunger, infectious diseases, education, gender equity (influenced by health and education) and environmental sustainability. The 2001 Human Development Report identified technical progress as the largest contributor towards reduced mortality rates and improved life expectancy in the period 1960-1990.

This report uses the case of genomics to show how emerging technology can be incorporated into a variety of approaches used to meet the MDGs. Illustrating its argument through examples, it demonstrates the urgent need for developing countries to harness new science for development. It describes initiatives to create a conducive science policy environment, an essential building block for strengthening capacity to absorb and implement new technologies, and human resources to encourage R&D, enterprise and growth. By highlighting the global public goods characteristics of the science, the report outlines the elements of a concrete action plan – the creation of a global partnership for multi-sectoral and multidisciplinary collaboration to promote genomics worldwide.

This report will be of interest to actors from several disciplines, ranging from scientists to policy-makers – they will find that it moves seamlessly from policy to science and back in a highly interdisciplinary way.

The completion of the Human Genome Project in April 2003 was celebrated with great fanfare, but its potential contribution to developing countries went unnoticed. Developing countries were conspicuous in their absence from Francis Collins' agenda in the April 24th, 2003 issue of *Nature*. This report brings developing countries into the limelight, and furthermore focuses on a coherent vision supported by a policy framework – innovation for development. Given Secretary-General Kofi Annan's call to world scientists to forge global alliances for achieving development goals, this is the right time to explore the issues discussed here. As an illustration, this report plays a crucial role in helping the international and national policy makers, stakeholders and development practitioners understand the ways in which science, technology and innovation can contribute to long-term improvement of human welfare and economic transformation in developing countries.

Calestous Juma

Co-coordinator

Task Force on Science, Technology and Innovation of the Millennium Project

Professor of the Practice of International Development

John F. Kennedy School of Government, Harvard University

Lee Yee-Cheong

Co-coordinator

Task Force on Science, Technology and Innovation of the Millennium Project

President of the World Federation of Engineering Organizations (WFEO)

AUTHORS OF THIS REPORT

Tara Acharya is a Research Associate for the Canadian Program on Genomics and Global Health. She contributed to the development of the concepts in this report and had overall responsibility for the research, analysis, writing and execution of this report.

Abdallah S. Daar is Professor of Public Health Sciences and Surgery at the University of Toronto. He directs the Program in Applied Ethics and Biotechnology and co-directs the Canadian Program on Genomics and Global Health at the University of Toronto Joint Centre for Bioethics. Together with Peter Singer and Elizabeth Dowdeswell, he initiated this work and participated in the writing and execution of this report.

Elizabeth Dowdeswell is President of the Nuclear Waste Management Organization and Visiting Professor of Public Health Sciences at the University of Toronto. She developed the concept of the Global Genomics Initiative, discussed in chapter 3, and provided editorial support.

Peter A. Singer* is Professor of Medicine, Sun Life Financial Chair and Director of the University of Toronto Joint Centre for Bioethics, and is Co-Director of the Canadian Program on Genomics and Global Health. He helped develop the concept for this report and oversaw all aspects of its execution.

Halla Thorsteinsdóttir is Assistant Professor of Public Health Sciences at the University of Toronto. She took part in drafting and providing editorial support of the report and helped develop concepts presented in chapters 3 and 4. She oversaw the study that identified the ten most important biotechnologies for improving health in developing countries, discussed in chapter 2.

* *Correspondence should be sent to:*
Peter A. Singer,
University of Toronto Joint Centre for Bioethics,
88 College Street, Toronto, Ontario, M5G 1L4, Canada.
Tel: 416 978 4756
Fax: 416 978 1911
Email: peter.singer@utoronto.ca

Canadian Program on Genomics and Global Health
University of Toronto Joint Centre for Bioethics

Date:
ISBN: # 0-7727-8762-X

ACKNOWLEDGEMENTS

We thank Calestous Juma, Lee Yee-Cheong, members of the United Nations Millennium Project's Science and Technology Task Force (Kamel Ayadi, Susan Brandwayn, Norman Clark, Denis Gilhooly, Qiheng Hu, Vijaya Kumar, Sanjaya Lall, Tony Marjoram, James Moody, Kenneth Nwabueze, Teresa Poon, Tony Ridley, Francisco Sercovich, Judith Sutz, Brendan Tuohy, Caroline Wagner) and Smita Srinivas for providing us with valuable guidance and suggestions in the preparation of this report. We also thank Richard Smith for his role in developing the concept of genomics as a global public good, Basma Abdelgafar, Lynn Mytelka and Uyen Quach for discussions relating to chapter 4, and Andrew Taylor for material relating to chapter 1. Robyn Kennedy and Elizabeth Martin participated in the preparation of the report. We owe special thanks to Archana Bhatt for her work in the final preparation, design, and execution of the report. We are also grateful to Douglas K. Martin, Shauna Nast and Alyna Smith for their work on a previous report on the "Top 10 Biotechnologies to Improve Health in Developing Countries". We thank Michael Keating for his editorial support.

The CPGGH receives most of its funding from the Ontario Research and Development Challenge Fund, and Genome Canada through the Ontario Genomics Institute. Matching partners for some of the projects include the Fogarty International Center, Food Biotechnology Communications Network, Food Systems Biotechnology Centre, GlaxoSmithKline, The Hospital for Sick Children, Indian Council for Medical Research, Industry Canada, International Development Research Centre (IDRC), the McLaughlin Centre for Molecular Medicine, Merck and Co, Mount Sinai Hospital, Sunnybrook and Women's College Health Sciences Centre, University of Guelph, University Health Network, University of Toronto, and the World Health Organization. Peter A. Singer is supported by a Distinguished Investigator award from the Canadian Institutes of Health Research.

EXECUTIVE SUMMARY

A century of innovation in science and technology, together with improvements in socio-economic conditions, has brought better health, longer lives and an improved quality of life for many. However, the benefits of modern medicine have still not reached billions of people in developing countries. Each year an estimated 11 million children die, mainly in developing countries, before reaching their fifth birthday, mostly from malnutrition or diseases that are considered easily preventable in the industrial world. The growing health crises, particularly in HIV/AIDS, malaria and tuberculosis, are reversing some of the gains of past decades. Average life expectancy is forecast to drop to less than 30 years in several countries in sub-Saharan Africa within a decade if nothing is done to reverse the trend. Meanwhile, in many industrial nations, the average person can look forward to more than 80 years of life.

Good health is essential not only for quality of life, but also for the social and economic development that is needed to alleviate poverty, which is at the root of many health problems. Genomics (the powerful new wave of health-related life sciences energized by the human genome project and the knowledge and tools it is spawning) is a relatively new field, but it has tremendous potential to address health problems in developing countries, if we rise to the challenge. This report explains how genomics and related health biotechnologies can improve global health, how the world can unite in a global approach to make it happen, and what steps developing countries themselves are taking to harness these technologies.

We see a strong connection between genomics and the United Nations Millennium Development Goals (MDGs). These eight goals were adopted by all UN members in 2000 in a commitment to promote sustainable development and eliminate poverty in the world. The first seven goals are directed at specific objectives in promoting development and improving people's lives, including health, while the eighth goal, developing a global partnership for development, focuses on how to achieve the objectives. The Millennium Project established task forces to come up with strategies to help developing countries achieve the MDGs. One of these is the Science and Technology Task Force, created because many of the MDGs cannot be realized without a strong contribution from science and technology.

Technologies such as genomics, including DNA sequencing and bioinformatics, once considered expensive, exotic and applicable only to wealthy nations, have been rapidly evolving. Some applications have become simpler and cheaper to the point that they can start replacing older technologies that are used for health care in poorer nations. Such simple and easy to use tests are being developed for TB, hepatitis C and other diseases. Recombinant vaccines, a result of genetic engineering, promise to be safer, cheaper and easier to store than traditional vaccines. Microorganisms with remarkable biochemical properties show promise of being able to reduce pollution, making water safer to drink.

The purpose of this report is to focus on the role of genomics and related health biotechnologies as an example of the application of science, technology and innovation to improve global health and contribute towards meeting the United Nations Millennium Development Goals (MDGs).

Genomics offers a powerful new set of tools to improve health globally. The science of genomics is generating vast amounts of new knowledge, which can be used creatively in the development of new diagnostic technologies, treatments and preventive programs. This means economic opportunities for developing as well as industrialized nations.

How can poorer nations get more access to genomics for development? Much genomics knowledge has been made public, so it can be considered a global public good, although private companies make use of this information to develop products and services. We need a governance mechanism that fosters a balance between the global public goods characteristics of genomics knowledge and the private goods nature of its application. We propose the

creation of a global partnership, the Global Genomics Initiative (GGI), to promote genomics for health. We see this as a global network of industry leaders, academics, concerned citizens, members of NGOs and government officials, with strong representation from the developing world.

Finally, our report tackles the challenge of how to put genomics and related technologies to work in developing countries within the next 5-10 years. We feel that developing countries with the scientific capacity and institutional arrangements that allow creation, utilization, adaptation or diffusion of genomics are well positioned to harness this new science for development. We see examples of strategies that some countries have followed to institute learning processes that can help them build their national systems of innovation in biotechnology.

The challenge we face is for industrialized and developing nations, and developing nations themselves, to build partnerships that will share the fruits of genomic knowledge, and thus help to build a better, healthier and more stable world. The conclusions of our report follow.

CONCLUSIONS

1. The development gap between developing countries and the industrialized world continues to grow. The international community is beginning to promote science and technology to reduce this gap. The genomics revolution holds tremendous potential to improve health in developing countries and, if harnessed appropriately, could help to reduce the development divide between North and South.

2. Genomics and related biotechnologies can help to achieve the United Nations Millennium Development Goals. Fast, accurate molecular diagnostic devices, safer recombinant vaccines, female-controlled vaginal microbicides and low-cost bioremediation tools are a few of the biotechnologies that can have an impact.

3. Genomics knowledge has the characteristics of a global public good. In order to harness the benefits of genomics for development, the developing world needs, above all, access to genomics knowledge.

4. The promotion of the science of genomics as a global public good and the encouragement of global knowledge flows could best be achieved through international partnerships. A Global Genomics Initiative (GGI) or international partnership of public and private entities from both North and South could catalyze genomics knowledge and learning worldwide.

5. Countries that have genomics capacity are best positioned to take advantage of the genomics revolution to meet their health needs. For the transfer of technologies to be effective and sustainable, they must be accompanied by transfer of science and knowledge. As well, receiving countries must have the capacity to absorb and use the technology.

6. Learning is important for building genomics capacity, and is central to the creation of National Systems of Innovation (NSI) in biotechnology in developing countries. These countries can strengthen the building blocks of the NSI framework through:

   a. Re-energizing academic institutions and public sector research to strengthen their science base.

   b. Training people and building human capital to use, adapt and innovate biotechnologies.

   c. Encouraging regional and international cooperation to create new channels for knowledge exchange and trade.

   d. Improving the policy environment (including intellectual property laws and regulation) to encourage the building of capacity.

   e. Fostering the growth of the private sector and encouraging it to address local health needs, and strengthening linkages between public and private sectors to create new biotechnology goods and services.

— CHAPTER ONE —

GENOMICS FOR HEALTH AND DEVELOPMENT

"The scientific community's basic concern for human welfare makes it an indispensable partner of the United Nations"

-Kofi Annan, 2003

Over the last 100 years, innovations in science and technology, together with improved socio-economic conditions, have resulted in improved health, quality of life and a vast increase in people's life expectancy worldwide. In light of this impressive record it is disheartening that the benefits of modern medicine still do not reach billions of people in the poorer parts of the world.[1] Children and adults are undernourished, live in poor housing with few modern facilities, such as clean, running water, and die from various, often preventable, illnesses in the prime of their lives. While there are many factors that come into play in the complex issue of development, it is widely accepted that science and technology plays a critical role in improving health in developing countries.[2]

Genomics[3] and related biotechnologies constitute an exciting new field of science that possesses tremendous potential to address health problems in developing countries – if we rise to the challenge. The purpose of this report is to focus on the role of genomics and related health biotechnologies as an example of the application of science, technology and innovation (STI) to improve global health and contribute towards meeting the United Nations Millennium Development Goals.[4]

The Millennium Development Goals (MDGs) grew out of the commitment of the United Nations to promote sustained development and eliminate poverty all over the world. They help quantify progress by defining targets and indicators to measure them. The first seven MDGs are directed at specific objectives in promoting development and improving people's lives, while the eighth goal, 'a global partnership for development', focuses on the means to achieve them. Many of the goals address health issues directly, such as improving infant and maternal health and reducing the prevalence of infectious diseases (see Table 1.1). The MDGs have become the international standard for measuring and tracking improvements in development. Therefore, the MDGs have the advantage of (i) agreement and support with the leaders of all UN member states, (ii) offering a comprehensive and multi-dimensional development framework, and (iii) setting clear quantifiable goals for all countries to meet by 2015. Although the MDGs, especially the health-related ones, have their critics, they do represent a standard by which progress may be measured.

The Millennium Project, whose mission is to devise and recommend operational frameworks to help developing countries achieve the MDGs, has set up ten thematically-oriented task forces, consisting of experts and leading practitioners. These task forces have carried out detailed and comprehensive research in each thematic area on the science, public health needs and medical interventions, as well as the social, political and economic issues. The goals of the Science and Technology Task Force are to address how science and technology can be enhanced and applied to help all countries achieve the MDGs. Its mission is guided by the understanding that most of the MDGs cannot be reached without a strong contribution from science and technology (Box 1.1).[5]

BOX 1.1 THE INTERIM REPORT OF THE SCIENCE AND TECHNOLOGY TASK FORCE

The interim report of the Task Force outlines approaches for using science, technology and innovation to achieve the MDGs. Meeting the goals will require a substantial reorientation of development policies to focus on key sources of economic growth, especially those associated with the use of new knowledge. Development involves the introduction of new knowledge into the economic system accompanied by institutional adaptation and continuous technological improvement. The report offers a conceptual framework under which economic change is viewed as a learning process by which knowledge is trans-

formed into goods and services through systemic interactions among various parts of the economy. The report states that governments need to facilitate technological learning, but it is in enterprises that the learning occurs, and where technological capability accumulates. It places particular emphasis on interactions among government, industry and knowledge-generating institutions to achieve the desired economic changes. The report lists four priority areas that require policy focus: managing technological innovation in a rapidly globalizing world; redefining infrastructure development as a foundation for technological innovation; building human capabilities with specific emphasis on the scientific, technological and engineering sciences through institutions of higher learning; and enhancing entrepreneurship though the creation and expansion of businesses (including the effective use of intellectual, human, financial and social capital). It recommends policy innovations needed to bring science and technology to the core of development efforts, particularly the strengthening of science and technology advice at the national level, and realigning the activities of international institutions to reflect the technological imperatives of the goals.

SOURCE: www.unmillenniumproject.org/documents/tf10interim.pdf

This report on genomics lends support to the findings of the Science and Technology Task Force by using genomics as an example of scientific technology and innovation for achieving the MDGs. The report describes ways in which genomics can help to meet the MDGs, and proposes a framework for action that places science, technology and innovation at the center of the development agenda.

TABLE 1.1: UNITED NATIONS MILLENNIUM DEVELOPMENT GOALS

Goal 1: Eradicate extreme poverty and hunger	Target 1:	Halve, between 1990 and 2015, the proportion of people whose income is less than one dollar a day
	Target 2:	Halve, between 1990 and 2015, the proportion of people who suffer from hunger
Goal 2: Achieve universal primary education	Target 3:	Ensure that, by 2015, children everywhere, boys and girls alike, will be able to complete a full course of primary schooling
Goal 3: Promote gender equality and empower women	Target 4:	Eliminate gender disparity in primary and secondary education, preferably by 2005, and to all levels of education no later than 2015
Goal 4: Reduce child mortality	Target 5:	Reduce by two-thirds, between 1990 and 2015, the under-five mortality rate
Goal 5: Improve maternal health	Target 6:	Reduce by three-quarters, between 1990 and 2015, the maternal mortality ratio
Goal 6: Combat HIV / AIDS, malaria and other diseases	Target 7:	Have halted by 2015 and begun to reverse the spread of HIV / AIDS
	Target 8:	Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases
Goal 7: Ensure environmental sustainability	Target 9:	Integrate the principles of sustainable development into country policies and programmes and reverse the loss of environmental resources
	Target 10:	Halve, by 2015, the proportion of people without sustainable access to safe drinking water
	Target 11:	By 2020, to have achieved a significant improvement in the lives of at least 100 million slum dwellers
Goal 8: Develop a global partnership for development	Target 12:	Further develop an open, rule-based, predictable, non-discriminatory trading and financial system
	Target 13:	Address the special needs of the Least Developed Countries
	Target 14:	Address the special needs of landlocked countries and small island developing states
	Target 15:	Deal comprehensively with the debt problems of developing countries through national and international measures in order to make debt sustainable in the long term
	Target 16:	In co-operation with developing countries, develop and implement strategies for decent and productive work for youth
	Target 17:	In co-operation with pharmaceutical companies, provide access to affordable, essential drugs in developing countries
	Target 18:	In co-operation with the private sector, make available the benefits of new technologies, especially information and communications

SOURCE: www.developmentgoals.org

Science, Technology and Innovation for Health and Development

The benefits of technology

Science, technology and innovation (STI) constitute a major force in modern times for development. Technology breakthroughs in the biomedical sciences during the 20th century have helped to remove many obstacles to development.[6] With the aid of science and technology, new opportunities have arisen in diverse aspects of peoples' lives: in increasing their productive capacity, improving health, simplifying communications and in controlling adverse effects of nature. For example, advances in biomedical sciences, such as vaccines and antibiotics, made it possible for East Asia and Latin America in the 20th century to improve the health of their populations and increase their life expectancy faster than it took Europe to do so in the 19th century.[7] This is supported by a World Bank study that shows that science and technology have accounted for a worldwide average drop in mortality rate of over 40% between 1960 and 1990.[8]

There is also some empirical evidence for the positive influence of S&T on economic development.[9] Development experts and policymakers tend to agree that investment in science and technology is important for economic growth and development (see Box 1.2). Although economists have not been able to establish a clear quantitative relationship between S&T and economic development, they have made observations that support the existence of one. Innovations fuelled by science and technology seem to be a determining factor in how competitive economies are (for developed countries).[10] The link between S&T investment and economic growth in developing countries appears to be more tenuous at present. An early example where S&T investment seems to have had a positive impact on economic growth is Japan, followed more recently by China, India and Brazil. Many policymakers in industrialized and developing countries accept that S&T, although not a 'magic bullet', is at least a component of sound economic development strategy.

BOX 1.2 INTER-ACADEMY COUNCIL ON SCIENCE AND TECHNOLOGY CAPACITY

The Inter-Academy Council on Science and Technology Capacity (IAC), chaired by Bruce Alberts, President of the U.S. National Academies of Science, was created in May 2000 to bring together international science academies to discuss the scientific aspects of problems of global concerns. The aim of this initiative was to develop a global strategy for promoting capacities in science and technology and the first report of the Council was recently presented to UN Secretary General Kofi Annan.[11]

This report builds on the view that mobilization of sound scientific knowledge and evidence-based principles is needed to address critical world issues such as poverty, disease, the effects of globalization and economic transformation. The report recognizes the importance of partnerships between the world's scientific communities to help bring the benefits of science and technology to all areas of the globe. By enhancing local S&T capacity, the benefits of science will connect national cultures in a way that eliminates the growing technology gaps between developed and developing nations. This report proposes a vision for every nation to develop an S&T strategy.

Among its key points:

- Science and technology can help achieve economic well-being and social justice. However there must be:

1) a national commitment by the public and private sectors to promote science and technology
2) a mechanism for providing S&T inputs into decision making
3) procedures for a broad dissemination of S&T knowledge.

- There is a critical need for problem-solvers to work together in an interdisciplinary and systems-level approach to deal with issues in such fields as science and technology, agriculture, engineering and medicine.

- Countries must create, maintain and continually modernize an educational base for training their youth to become the new generation of scientists and engineers.
- Countries need research institutions for S&T capacity, including: autonomous centers of excellence, strong universities, virtual networks of excellence and independent national or regional academies of science, engineering and medicine.
- For-profit organizations are the world's predominant force in using S&T for the production and distribution of new goods and services. It is important to create an enabling environment for business, so the private sector can build S&T capacity that will lead to economic growth in developing nations.
- Both industrialized and developing nations need to commit themselves to building funding mechanisms to develop the S&T capacities of developing nations.
- Achieving these goals require collaboration among a wide range of actors at the international level.

The report provides a vision for increasing S&T capacity in developing countries by strengthening the building blocks of innovation systems through: 1) national policies that nurture a nation's S&T capacity and, 2) an international coalition that promotes knowledge flows from developed to developing nations.

SOURCE: http://www.interacademycouncil.net/reports.asp

THE NEED FOR GOOD HEALTH

Despite the positive influence of modern science and technology on life expectancy and health, in recent years the world has seen an alarming rise in the incidence of infectious diseases, particularly HIV/AIDS. In many sub-Saharan African countries life expectancy had been rising during most of the last century but has actually *fallen* in recent times due to the AIDS crisis.[12] New technologies to deal with this, and other infectious diseases, are in high demand but are still unavailable.

It is no surprise that most people in the world view good health as a pre-requisite for quality of life. Good health is crucial for survival and is essential for productivity and therefore for social and economic development. The Commission on Macroeconomics and Health showed that the linkages of health to poverty reduction and to long-term economic growth are powerful.[13] Empirical evidence suggests that countries with low levels of health and education have a much more difficult time achieving sustained economic growth than countries with higher levels of health and education. Even after controlling for the effect of macroeconomic variables such as structural characteristics of the economy, health status continues to explain an important percentage of the differences in economic growth between countries.[14, 15, 16]

Investing in health is therefore an effective strategy to boost economic development and contribute to the efforts to meet the Millennium Development Goals. According to the Commission on Macroeconomics and Health, most governments in developing countries and the international donor community have seriously underestimated the value of investing in health. To make the case for investing in health, it estimated that approximately 330 million disability-adjusted life years (DALYs - one disability-adjusted life-year is defined as the loss of one year of healthy life to disease) could be saved for every 8 million deaths prevented, generating economic benefit of US$186 billion per year as of 2015. This would require additional annual health outlays, for all low-income countries and selected middle-income countries, of US $57 billion by 2007 and US $94 billion by 2015.[13]

Investing in health provides the resources to develop and enhance tools to address health problems of people in developing countries. One current obstacle to developing such tools is that most ongoing health research is largely aimed at health problems in richer countries. Ninety percent of all health research expenditure is targeted at problems affecting only ten percent of the world's population - the so-called "10/90 gap".[17] As an illustrative example, of

the 1,223 new drugs introduced to the world market between 1975 and 1996, only 13 were aimed specifically at treating tropical diseases.[6]

The Potential of Genomics

Medicine and the biomedical sciences are currently in the midst of a fundamental change that is fueled by the genomics revolution. In its report on "Genomics and World Health" the World Health Organization's Advisory Committee on Health Research observed that the application of knowledge gained from the characterization of the genomes of organisms holds enormous potential for the development of new health care innovations over the coming decades.[18] With increased understanding of the molecular basis of diseases and their causation, the way we identify, prevent, diagnose, and treat diseases in the new millennium is bound to change.

The science of genomics is generating vast amounts of new knowledge. Once generated, this knowledge can be used creatively in the development of new diagnostic technologies, treatments and preventive programs.

BOX 1.3 GENES AND GENETICS; GENOME AND GENOMICS

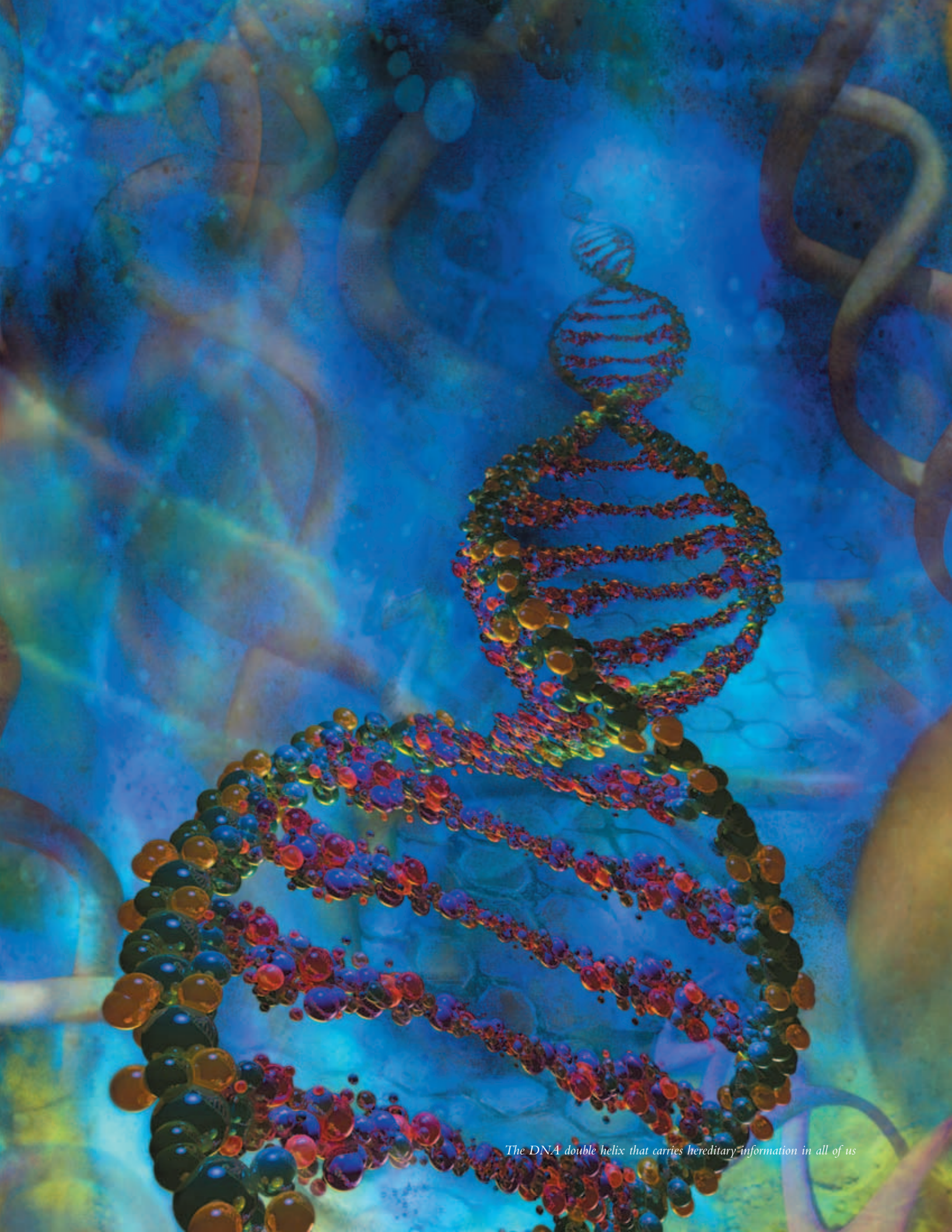
Genes carry information about physical and functional inheritance vertically between generations. They are composed of deoxyribonucleic acid (DNA), arranged in the famous 'double helix', which carries the genetic instructions for making living organisms, establishing how a particular organism with its own unique characteristics will be formed.[19a, b] Although genes carry hereditary information, it is the interactions of genes both with each other as well as with the environment that determine the phenotype. The field of *genetics* generally refers to the study of genes – most often of single genes, or a small number of genes – to determine the specific roles of these genes in diseases or in physical characteristics of an individual organism.

The *genome* refers to an organism's *entire* genetic material, that is, their complete set of DNA contained in each cell.[20] The human genome is therefore the genetic material that 'makes' a human, estimated at between 30,000 and 40,000 genes.[21a, b] The science of *genomics*, therefore involves the examination of an organism's entire set of genes and their interactions in a comprehensive analysis of the genetic components of organisms. This covers *structural* genomics, the 'mapping' and 'sequencing' of the entire genome of an organism, and *functional* genomics, which seeks to understand the function and interaction of genes.[22]

In this report, we refer to genomics as the powerful new wave of health related life sciences energized by the human genome project and the knowledge and tools and scientific fields it is spawning. These include, for example, bioinformatics and proteomics.

Genomics requires massive amounts of information to be collected and analysed. The field has evolved over the last few decades in large part due to advances in sequencing technology, as well as information and communication technology. Automated DNA sequencing and genotyping have made it possible to characterize rapidly large numbers of genes. The means to manage, store and process enormous databases of biological information have spawned an entirely new field – bioinformatics.[23, 24]

These developments hold tremendous promise for the prevention, diagnosis and treatment of some of the major diseases affecting humankind, including HIV, malaria, and tuberculosis, as well as non-communicable diseases such as diabetes, cancer and cardiovascular disease. Genomics can also be applied to understand the genetics of bacteria, plants, and animals. Many genomes have been sequenced and mapped. In fact, the first genome sequence (that of *H. influenzae*) was completed in 1995, by researchers at The Institute for Genomic Research (TIGR).[25] The sequence was a mere 1.8 million base-pairs, compared with the 3.2



The DNA double helix that carries hereditary information in all of us

billion base-pairs of the human genome. Many other genomes of the plant and animal kingdom have been sequenced, ranging from common yeast to rice, and all these sequencing achievements promise to enhance scientific knowledge. In October 2002, scientists published the sequence of the parasites responsible for human malaria, *Plasmodium falciparum*, as well as the mosquito that carries it, *Anopheles gambiae*.[26] The knowledge of these genomes, together with the knowledge of the human genome, can be used to develop new drug and vaccine targets against malaria. Genomics can be applied in a wide range of products, which we will describe in further detail in Chapter 2.

BOX 1.4 THE HUMAN GENOME PROJECT

The best-known genomics project is the Human Genome Project that began in 1990 and was largely completed in April 2003. This is a large-scale global project, involving research teams in 20 different countries, allocated over US $3 billion in public sector funding alone.[27] It arose from the need for a global approach to tackle the enormous and complex task of sequencing the 3.2 billion bases in the human genome. This concerted effort resulted in the sequencing of 94% of the human genome by February 2001, and complete sequencing in April 2003, two years earlier than in the original plan.[28] This acceleration was at least partly due to competition from Celera, a private biotechnology company based in Rockville, Maryland. In 1998, Celera challenged the Human Genome Project to a duel, claiming that it would use a faster sequencing method (the 'shotgun' method) and novel computer algorithms to complete the human genome sequence by 2003. One of the criticisms against Celera was that the data it generated were only accessible through private subscription. On the other hand, the public venture made the data available without restrictions within 24 hours of assembly.

There may also be direct *economic* benefits of genomics. It is already a significant contributor to the biotechnology sector.[29] Despite early setbacks, the genomics-based pharmaceutical market was expected to grow from US $2.2 billion in 1999 to US $8.2 billion in 2004.[6] The major economic players in the world are not the only ones expected to benefit from genomics. Cuba, for example, has invested heavily since the 1980's in research infrastructure and manufacturing in biotechnology. As a result biotechnology is poised to become a major export industry in Cuba.[30]

In order to reap direct economic benefit from genomics, countries will have to be active participants in the development and manufacturing of genomics products. Those countries that will benefit the most from genomics are those that have appropriate health products to improve the health of their populations and who are active in developing and supplying those products. This will involve engaging and stimulating the private sector, without which the production and commercialization of new biotechnology products will be a challenge. As highlighted by the UN Commission on Private Sector and Development report, "*Unleashing Entrepreneurship: Making Business Work for the Poor*," the process of commercialization for development involves the dissemination and facilitation of knowledge flows between public and private sectors of both developed and developing markets.[31] The report recommends action in both the public and private spheres, but also emphasizes the linkages between these spheres, recognizing the importance of cooperation and partnerships to achieve goals (Box 1.5).

BOX 1.5 THE REPORT OF THE UN COMMISSION ON PRIVATE SECTOR AND DEVELOPMENT

The Commission on the Private Sector and Development (co-chaired by Canadian Prime Minister Paul Martin and former Mexican President Ernesto Zedillo) has presented a report titled

"*Unleashing Entrepreneurship: Making Business Work for the Poor*" to UN Secretary-General Kofi Annan. The objective of the Commission was to identify the legal, financial, and structural obstacles blocking the expansion of the indigenous private sector in developing countries, with a special focus on the poorest regions and communities. The report calls for targeted policy reforms and other initiatives that would spur growth in the local businesses that are critical to the eradication of poverty in the developing world.

Chapter 1 describes the importance of the private sector in alleviating poverty. Through sustained economic growth, employment within the domestic private sector can flourish and provide the key link between growth and poverty alleviation in developing countries.

Chapter 2 outlines three major structural challenges that confront the private sector in developing countries: 1) Micro-enterprises and many small and medium enterprises (SMEs) operate informally; 2) Many SMEs have barriers to growth; 3) A lack of competitive pressure shields larger firms from market forces and from the need to innovate. This chapter also emphasizes the need for a strong foundation in the global and domestic macro environments, physical and social infrastructure and rule of law when building a private sector. Chapter 3 focuses on specific actions that are needed to foster the rule of law and to create a level playing field for entrepreneurship, as well as to improve access to financing and the availability of skills and knowledge. It notes that a level playing field, access to finance, and knowledge and skills are key factors within the domestic private sector.

Chapter 4 provides an analysis of how better to engage the private sector in addressing the development challenge. Through private actions and public-private partnerships the power of linkages and networks will increase the potential for sustainable development, improving corporate governance and advancing corporate social responsibility standards.

Chapter 5 outlines recommended actions within three areas: Public Sphere: Promote the reform of laws, regulations and other barriers to growth.

Public-Private Sphere: Facilitate cooperation and partnerships between public and private players to enhance access to such key factors as financing, skills and basic services.

Private Sphere: Encourage the development of business models that can be scaled up and copied and that are commercially sustainable.

The Commission intends to see its recommendations put into practice, unleashing the full economic and social potential of small and medium-sized businesses employing and serving the world's poor.

SOURCE: http://www.undp.org/cpsd/

Bridging the Genomics Divide

Genomics has the potential to benefit both developing and industrialized countries. The term genomics no doubt evokes images of sequencing laboratories at Stanford or Cambridge, or biotechnology companies like Celera or Human Genome Sciences. But these images do not have to be specific to industrialized countries. There is no reason why genomics should not also conjure up visions of venture capital firms in India, laboratories in Brazil and biotechnology firms in South Africa. The WHO Advisory Committee on Health Research stresses that the proven benefits from this field should be made available to developing countries. So far, most biotechnologies are being applied primarily to health problems in industrialized countries, creating concern that the world is witnessing the formation of a 'genomics divide' between North and South.[32] If unchecked, this inequity could lead to even greater disparities in health, as wealthier countries become healthier, and the spread of infectious disease, the rise in chronic illness and persistent environmental pollution continue to degrade health and hold back progress in developing countries. It is therefore timely to focus on whether, and how, genomics can make major contributions towards meeting the Millennium Development Goals.

One recent initiative that aims to leverage basic science and engage the world's best scientific minds in global health is the Grand Challenges in Global Health program, sponsored by the Bill and Melinda Gates Foundation, and administered by the Foundation for the National Institutes of Health (Box 1.6).[33]

BOX 1.6 GRAND CHALLENGES IN GLOBAL HEALTH

On January 26, 2003, at the World Economic Forum in Davos, Switzerland, Bill Gates announced a $200-million medical research initiative, the Grand Challenges in Global Health.

A grand challenge was described as, "a call for a specific scientific or technological innovation that would remove a critical barrier to solving an important health problem in the developing world with a high likelihood of global impact and feasibility." A grand challenge is distinct from one of the many "big problems" in global health, such as HIV/AIDS, malnutrition, the lack of access to medical care, or the lack of adequate resources. A grand challenge is meant to direct investigators to a specific scientific or technical breakthrough that would be expected to overcome one or more bottlenecks in an imagined path toward a solution to one or preferably several significant health problems.

The efforts to identify Grand Challenges in Global Health relied on financial and administrative resources of two collaborating foundations, the BMGF and the Foundation for the National Institutes of Health (NIH); a selection panel (scientific board) of 20 scientists and public health experts from 13 countries, including several from the developing world; and on the scientific community to supply ideas for challenges. This policy forum also outlined the next steps that will be taken to fund research and address those challenges in subsequent years.

Following the announcement of the Grand Challenges, the Foundation for NIH issued a Request for Proposals to address each of the challenges with grants of up to a total of $20 million over five years or less. How many grants will be made toward each challenge and how many of the 14 challenges will have funded grants will depend on the quality of the proposals and the available resources.

Applications will be invited from anywhere in the world, from one or multiple institutions or countries in the developed or developing world, and from non-profit and for profit institutions. The Foundation for NIH will oversee the application and award processes, will encourage the participation of developing-country researchers and will be available to advise about organizing inter-institutional or international consortia where appropriate.

The scientific board expects to continue to seek candidate challenges through new solicitations of ideas, the convening of workshops with invited speakers on defined topics, and continued discussion among members of the board. In the very design of its gift, the BMGF has challenged the world's scientists to produce a program that has the potential to improve the lives of many people.

Within three months of the Call for Ideas in May 2003, 1,048 submissions were received from scientists and institutions in 75 countries.

Goals and Grand Challenges

To improve childhood vaccines:

GC 1: Create effective single-dose vaccines that can be used soon after birth;
GC 2: Prepare vaccines that do not require refrigeration;
GC 3: Develop needle-free delivery systems for vaccines.

To create new vaccines:

GC 4: Devise reliable tests in model systems to evaluate live attenuated vaccines;
GC 5: Solve how to design antigens for effective, protective immunity;
GC 6: Learn which immunological responses provide protective immunity.

To control insects that transmit agents of disease:

GC 7: Develop a genetic strategy to deplete or incapacitate a disease-transmitting insect population;

GC 8: Develop a chemical strategy to deplete or incapacitate a disease-transmitting insect population.

To improve nutrition to promote health:

GC 9: Create a full range of optimal bioavailable nutrients in a single staple plant species.

To improve drug treatment of infectious diseases:

GC 10: Discover drugs and delivery systems that minimize the likelihood of drug resistant microorganisms.

To cure latent and chronic infections:

GC 11: Create therapies that can cure latent infections;

GC 12: Create immunological methods that can cure chronic infections.

To measure disease and health status accurately and economically in poor countries:

GC 13: Develop technologies that permit quantitative assessment of population health status;

GC 14: Develop technologies that allow assessment of individuals for multiple conditions or pathogens at point-of-care.

SOURCE: www.grandchallengesgh.org

Governments of industrialized countries can also take steps to spread the benefits of science and technology. Canada is one country that has pledged action to harness its R&D capabilities to address global problems (Box 1.7).

BOX 1.7 CANADA'S COMMITMENT TO S&T FOR DEVELOPMENT

The Canadian federal government has invested over $13 billion (Canadian) in the past six years in innovation initiatives such as the creation of new research institutions and programs like the Canadian Foundation for Innovation, the Canada Research Chairs, Genome Canada and the Canadian Institutes for Health Research. These initiatives complement the work of such well-known institutions as the International Development Research Centre. Current annual funding for R&D for development is approximately one per cent of Canada's total annual R&D expenditures. In the Speech from the Throne in February 2004, the federal government said that Canada is a knowledge-rich country. "We must apply more of our research and science to help address the most pressing problems of developing countries." In his reply to the Speech from the Throne, Prime Minister Paul Martin said: "Our long-term goal as a country should be to devote no less than five per cent of our R&D investment to a knowledge-based approach to develop assistance for less fortunate countries."

SOURCE: www.pm.gc.ca/eng/

Genomics cannot solve all health and development problems, but a balanced approach is a more pragmatic strategy, where conventional public health approaches are combined with genomics-based technologies wherever feasible and practical. The case of malaria is a good example. Conventional methods to control malaria include bed nets treated with insecticide, or covers on open drains to limit mosquito breeding. These methods can be used in combination with new approaches to malaria control, such as new malaria vaccines and drugs (currently in clinical trials) and genetically altering mosquitoes to block the cycle of parasite transmission.

Similarly, it is unlikely that achieving good health will solve all the problems associated with poverty. Development is not an automatic process but requires a careful, considered approach that stimulates many factors simultaneously. One such comprehensive approach would be to invest in established indicators of development - education, living conditions, infrastructure, and improved governance - as well as new and emerging technologies like genomics. The dire conditions in developing countries require us to focus on all possible tools to promote health and development. The potential of genomics and other modern health biotechnologies are so compelling that they should be seriously considered to be an integral part of a sound overall development strategy. Therefore, there is good reason to evaluate the contributions genomics and other modern health biotechnologies can make to achieving the UN Millennium Goals.

— CHAPTER TWO —

GENOMICS AND THE MILLENNIUM DEVELOPMENT GOALS

In the previous chapter, we discussed the relevance of science and technology to health and development. In this chapter, we examine specific examples of how new biotechnologies can help to meet the Millennium Development Goals (MDGs). Some of these examples are described in a recent publication on biotechnology solutions for the UN Millennium Development Goals.[34]

The MDGs are the eight development targets that all 189 Member States have committed to achieving by 2015 (Box 2.1). We will highlight the relevance of genomics and related biotechnologies to the achievement of the MDGs by examining the top 10 biotechnologies that are likely to improve health in developing countries within the next five to ten years (Box 2.2).[35] These 10 biotechnologies were identified in a technology foresight study conducted by the University of Toronto in partnership with scientists who have expertise in health and biotechnology and in-depth knowledge about public health problems of developing countries. After describing the methodology that was used to prioritize these biotechnologies, we will describe each technology in turn and identify ways in which it is, or could be made, relevant to specific MDGs. Table 2.1 shows a brief summary of this information.

BOX 2.1 MILLENNIUM DEVELOPMENT GOALS

1. Eradicate extreme poverty and hunger
2. Achieve universal primary education
3. Promote gender equality and empower women
4. Reduce child mortality
5. Improve maternal health
6. Combat HIV / AIDS, malaria and other diseases
7. Ensure environmental sustainability
8. Develop a global partnership for development

BOX 2.2 TOP 10 BIOTECHNOLOGIES

1. Molecular diagnostics
2. Recombinant vaccines
3. Vaccine and drug delivery
4. Bioremediation
5. Sequencing pathogen genomes
6. Female-controlled protection against sexually transmitted infections
7. Bioinformatics
8. Nutritionally enriched genetically modified crops
9. Recombinant therapeutic proteins
10. Combinatorial chemistry

Methodology of the Biotechnology Prioritization Study

The members of the Scientific Panel for the "Top 10 Biotechnologies" study were identified through literature searches and with the recommendations of individuals at the World Health Organization and Rockefeller Foundation. We invited 39 scientists from both developing and developed countries to take part in the study with 28 scientists completing the project.

We used a structured process known as the Delphi method to bring the Panel to a consensus regarding the identification and ranking of the biotechnologies.[41] The study spanned three "rounds," which were completed over a period of five months through emails, faxes, phone calls and personal interviews.

In Round 1, we invited the 39 scientists, with 30 accepting the invitation, to participate in the project and asked them the open-ended question, "What do you think are the major biotechnologies that can help improve health in developing countries within the next 5 to 10 years?" We analyzed and organized their answers according to common themes (e.g. diagnostics, drug development, delivery

TABLE 2.1 HARNESSING THE MDGS WITH BIOTECHNOLOGY

MILLENNIUM DEVELOPMENT GOAL	STATISTICS / FACTS	BIOTECHNOLOGY TO ADDRESS MDG
Goal 3: Promote gender equality and empower women	In 2001 55% of HIV+ in sub-Saharan Africa were women Average HIV infection rates in teenage girls 5 times higher than those in teenage boys[36]	• Female control over STD transmission protection • Vaccine and drug delivery
Goal 4: Reduce child mortality	~ 11 million children die before reaching their fifth birthday[37]	• Molecular Diagnostics • Vaccine and drug delivery • Recombinant vaccines • Female control over STD transmission protection • Nutritionally enriched genetically modified (GM) crops • Combinatorial chemistry
Goal 5: Improve maternal health	Over 500,000 maternal deaths per year[36]	• Molecular Diagnostics • Vaccine and drug delivery • Recombinant vaccines • Female control over STD transmission protection • Nutritionally enriched GM crops • Combinatorial chemistry
Goal 6: Combat HIV, malaria and other diseases	HIV / AIDS, malaria and TB responsible for ~ 40% (5 million) of all deaths in developing world[38] In 2002, 3.1 million people died of AIDS, 2 million of TB, over 1 million of malaria [39]	• Molecular Diagnostics • Vaccine and drug delivery • Recombinant vaccines • Female control over STD transmission protection • Bioremediation • Sequencing pathogen genomes • Bioinformatics • Nutritionally enriched GM crops • Combinatorial chemistry
Goal 7: Ensure environmental sustainability	5 million deaths per year can be attributed to waterborne diseases[40]	• Bioremediation

systems), and generated a list of 51 distinct biotechnologies rather than our own preconceptions. As the list was being developed, it was reviewed and modified by three scientists (not members of the Panel) to ensure the technologies were mutually exclusive and categorized appropriately.

In Round 2, we sent the list of 51 biotechnologies to the Panel. We asked them to rank the ten most promising technologies and to provide reasons for their choices. Thirty scientists completed Round 2. To analyze the data, we combined their rankings (1st=10 points, 2nd=9pts, etc.) and produced a total point score for each technology. We also summarized the reasons provided by the panelists. The panelists made their decisions based broadly on the following six criteria:

- **Impact** - How much difference will the technology make in improving health?
- **Appropriateness** - Will it be affordable, robust and adjustable to health care settings in developing countries, and will it be socially, culturally and politically acceptable?
- **Burden** -Will it address the most pressing health needs?
- **Feasibility** - Can it realistically be developed and deployed in a time frame of 5–10 years?
- **Knowledge gap** - Does the technology advance health by creating new knowledge?
- **Indirect benefits** - Does it address issues such as environmental improvement and income generation that have indirect, positive effects on health?

In the final, consensus-building round, we sent a list of the top 12 technologies, based upon the Round 2 rankings, to the panelists along with a summary of the reasons they had provided in Round 2, with the opportunity to revise their ranking in light of this input. Twenty-eight panelists completed Round 3. The results of the final round represent the top 10 biotechnologies (Box 2.2) for improving health in developing countries in the next five to ten years. The top three technologies showed a high degree of consensus: all but one of the panelists included at least one of these among their personal top choices.

Top 10 Technologies Mapped onto the UN Millennium Development Goals

Each of the 10 technologies that emerged from the above study is presented below, accompanied by a snapshot of the Millennium Development Goals that it relates to. We have included illustrative examples, and emphasized technologies that are well-positioned to have a positive impact on the health needs of developing countries over the next five to ten years.

1. MOLECULAR DIAGNOSTICS

- Combat HIV/AIDS, malaria and other diseases
- Reduce child mortality
- Improve maternal health

Molecular diagnostics draw upon recent advances in biology to diagnose infectious disease by detecting the presence or absence of pathogen-associated molecules, such as DNA or protein, in a patient's blood or tissues. They present a powerful set of methods to address the health-related Millennium Development Goals, ***Combat HIV/AIDS, malaria and other diseases, Reduce child mortality, Improve maternal health***. Infectious and parasitic diseases are responsible for nearly 40%, or 17 million of all deaths every year. The three major killers are HIV/AIDS, malaria and tuberculosis, which together claim at least 5 million lives a year.[39] Each year an estimated 11 million children still die before reaching their fifth birthday.[37]

While improving public health infrastructure for disease prevention is crucial to the achievement of this goal, it is also true that once disease strikes, diagnosis and treatment methods are essential. Rapid and accurate diagnosis not only increases chances of survival, but also avoids waste of resources on inappropriate treatments and helps contain dis-

ease. It is not surprising that the scientific panel in the University of Toronto study ranked molecular diagnostics as the most promising set of technologies for improving health in developing countries over the next five to ten years.

Many of the diagnostic tools currently in use in developing countries are cumbersome, time-consuming and expensive. In contrast, molecular diagnostics are simple to use, give quick results and can be relatively cheap. In the following discussion, we focus on a few such technologies: polymerase chain reaction, monoclonal antibodies and recombinant antigens.

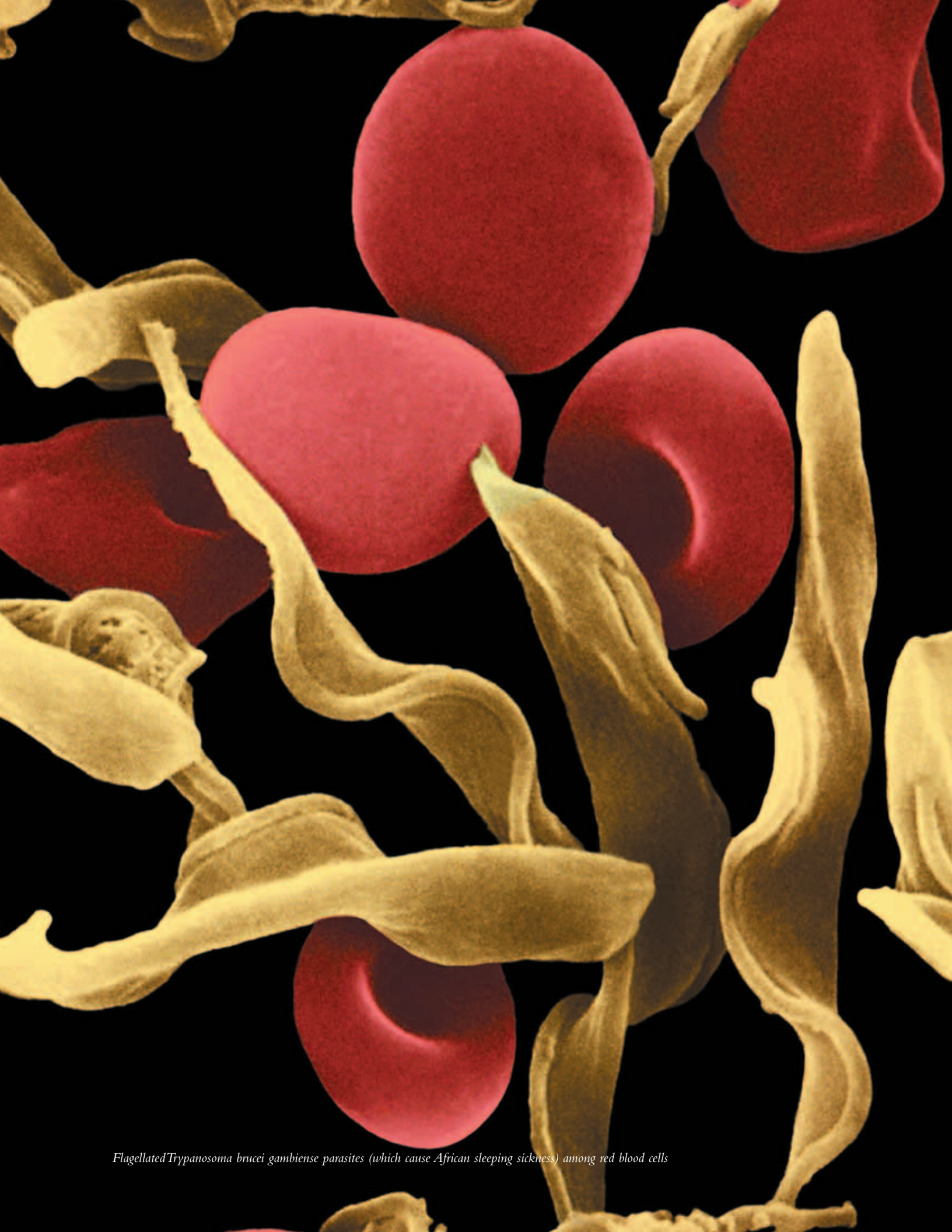
The *polymerase chain reaction* (PCR) is a quick way of making millions of copies of a specific sequence of DNA. This technology is fast and accurate. It takes advantage of the fact that organisms have unique genetic sequences. Amplification and identification of a pathogen-specific DNA sequence in the body fluids or cells of a person identifies infection in that individual. Besides being extremely sensitive, PCR tests can provide results in a few hours as opposed to days for culturing methods. They can also be used to detect infectious organisms that are difficult or impossible to grow in culture (e.g. tuberculosis, malaria) or are dangerous to handle (e.g. HIV/AIDS).[42]

BOX 2.3 BRANCHED DNA TEST

Genes unique to a pathogen can be used to identify the presence of the pathogen and therefore to diagnose infection. In a "branched DNA test", a patient's blood sample is treated with DNA "probes" designed to bind to genes unique to the pathogen. In order to detect the binding of the probe to the pathogen's genes, additional compounds that bind to the probe are added, forming a branched structure that emits a detectable signal such as light. A simple branched DNA test has been used with success in the diagnosis of African sleeping sickness.[43]

In the industrialized world, the use of PCR tests in the diagnosis of infectious diseases is increasing. Tests for HIV-1, gonorrhea, pneumonia and herpes are already available. Recent advances are beginning to bring this powerful tool within reach of the developing world. For example, a group involved in the testing of infants for HIV-1 successfully processed and stored blood samples for up to several months on commercially available filter paper.[44] A PCR test for three complexes of New World *Leishmania* (*Leishmania braziliensis*, *Leishmania mexicana*, and *Leishmania donovani*) – which cause a spectrum of diseases – was developed in Nicaragua and uses a technique known as multiplexing to test for more than one disease at once, saving both time and resources.[45] Going a step beyond current practices in PCR are new *nanotechnology* methods for detecting infection at the molecular level, without the need for DNA amplification. One nanotechnique uses gold particles complexed with diagnostic DNA fragments that have the ability to bind to specific pathogen-associated DNA sequences. A sample of the patient's blood is placed between two tiny electrodes in the presence of the probe. When the probe and its target DNA sequence match, the gold particles close the circuit between the electrodes and produce a detectable signal. Not only is this approach more sensitive than conventional detection methods, it has the potential to be substantially more affordable.[46]

While PCR tests are on their way to finding applications in developing countries, antibody-based applications are already highly suited to the developing world. *Antibodies* are molecules produced by the immune system in response to infection. They recognize and bind to proteins produced by pathogens. These proteins are known as antigens. Antibodies are specific, i.e. every antibody recognizes and binds to a specific type of antigen. This makes them an excellent tool for the diagnosis of infectious disease. In the last few years, the development of simple and rapid antibody-coated dipstick tests have increased the relevance of this technology for the developing world. Dipsticks can be used anywhere,



FlagellatedTrypanosoma brucei gambiense parasites (which cause African sleeping sickness) among red blood cells

without the need for laboratory facilities, running water or electricity. OptiMAL® is one of several antibody-based dipstick tests for malaria.[47] During a malaria outbreak in Honduras, it rivaled the accuracy of microscopic analysis, the "gold standard" of malaria diagnosis.[48] The Program for Appropriate Technology in Health,[49] an international not-for-profit organization committed to improving global health, has developed an HIV dipstick test that is now being produced by several private firms in developing countries. *Determine HIV-1/2* can diagnose both HIV-1 and HIV-2 based upon a reaction on a nitrocellulose strip between recombinant antigens and patient antibodies. The test is accurate and sensitive and has been successfully tested in the field in Ghana.[50] PATH is also developing dipsticks for the detection of malaria, TB and hepatitis C, among other diseases. Quidel has developed a dipstick test for *Streptococcus pneumoniae*, the most common cause of pneumonia.[51]

Monoclonal antibodies (mAb) are extremely specific antibodies. They are superior to antibodies harvested from human or animal serum because they are extraordinarily pure, show very high binding specificity and can be grown in large quantities. The drawback is that mammalian cell culture is expensive, so although the sensitivity and specificity of monoclonal antibodies are high, cost issues have prevented their widespread use in developing countries.

BOX 2.4 THE MONOCLONAL ANTIBODY CULTURE TECHNIQUE

The technique of monoclonal antibody culture involves three broad steps. The first step is to immunize a mouse with an antigen. When the mouse begins to produce antibodies to the antigen, its spleen is removed. Antibody-producing cells from the spleen are then fused with tumor cells (which grow and divide in vitro and are 'immortal'). Each hybrid cell produces identical antibody molecules. By allowing the hybrid cells to multiply in culture, it is possible to produce a population of cells, each of which produces identical antibody molecules. These antibodies are called "monoclonal antibodies" because they are produced by the identical offspring of a single antibody-producing cell. The new fused cell can also be re-injected into another mouse. This mouse produces pure monoclonal antibodies. The use of monoclonal antibodies for the diagnosis of infectious disease dates back to the early 1980s.[52]

Plantibodies are monoclonal antibodies that are produced in genetically engineered plants and then extracted for medical use. They are a cheaper source of antibodies than those produced in mammalian cells. One estimate places the cost of a gram of plantibodies at less than 5% that of mammalian cell monoclonal antibodies.[53] Another advantage is that they do not risk spreading animal diseases to humans. Plantibodies have been patented by Epicyte, a U.S. biotechnology company which plans to begin clinical trials of its anti-Herpes Simplex Virus 1 and 2 plantibody mixture, HX8.[54] The company was recently awarded a grant from the US National Institutes of Health for the development of plantibodies against Human Papilloma Virus (HPV),[55] which causes cervical cancer. Other companies have begun human trials of plantibodies for Hepatitis B, sexually transmitted diseases, and non-Hodgkin's lymphoma.

BOX 2.5 A NEW TEST FOR TUBERCULOSIS

New developments in diagnostic testing for tuberculosis indicate the diverse ways in which scientists are using the immune system for detecting the presence of pathogens in the blood.

A major obstacle to controlling tuberculosis is the lack of a reliable diagnostic blood test. The treatment of TB relies upon the identification of tuberculosis infection by targeted tuberculin skin testing, the main drawback of which is low specificity. For example, the BCG vaccination and environmental mycobacterial exposure can both result in false-positive results.

In response to this shortcoming, researchers at Oxford University and the Wellcome Trust have developed a new test. This test targets cells in the blood that are produced by the immune system, called T-cells. The presence of specific T cells, detected by the rapid ex-vivo enzyme-linked immunospot (ELISPOT) assay for interferon-gamma, is a highly sensitive and specific indicator of infection in patients who have tuberculosis; its sensitivity is substantially higher than that for the skin test. This test is set to supersede the tuberculin skin test and improve the control and prevention of this resurgent disease. The test is simple, quick, and not confounded by TB vaccination. Doctors hope it will supersede the skin test in the next few years and transform the way TB is diagnosed and controlled.[56]

As mentioned earlier, pathogen cells are associated with distinguishing molecules known as antigens, and antibodies can be used to detect the presence of antigens in a person's bloodstream. Similarly, antigens can also be used to detect antibodies. *Recombinant antigens* are genetically-engineered antigens mass-produced by fast-replicating organisms such as bacteria or yeast. (The term recombinant refers to the DNA produced when genetic information from more than one organism is 'recombined' in a laboratory process to form a hybrid molecule. A desired antigen is produced by incorporation of its DNA sequence into the DNA of a host bacterial cell). Like monoclonal antibodies, recombinant antigens also feature in simple handheld test devices capable of providing a diagnosis in a matter of minutes. These devices are particularly well suited to developing areas where clean water and electricity are not always accessible and people might have to travel significant distances to reach a medical facility.

2. RECOMBINANT VACCINES

- Reduce child mortality
- Improve maternal health
- Combat HIV / AIDS, malaria and other diseases

Recombinant vaccines can play an important part in achieving the fourth Millennium Development Goal, ***Reduce child mortality*** as well as to the fifth and sixth MDGs, ***Improve maternal health*** and ***Combat HIV/AIDS, malaria and other diseases***. The hepatitis B vaccine saves the lives of millions of people, including children, every year, and many HIV vaccine candidates currently under investigation are recombinant vaccines.

Vaccines stimulate the body to produce a protective immune response and thereby reduce the likelihood of serious infection. They are arguably the most important medical advance of the last hundred years. Vaccination has resulted in the eradication of smallpox, the imminent eradication of polio, and a dramatic reduction in the prevalence of many other infectious diseases.[57] Advances in vaccine research are expected to have an impact not only on communicable diseases, but also on non-communicable ones such as cancer.

Until a few decades ago, all vaccines consisted of either killed or inactivated ('attenuated') pathogens. Injection of this into a person would stimulate the person's immune system to produce antibodies against the foreign organism, thus conferring resistance to the pathogen in future infections. However, pathogen inactivation may sometimes be insufficient, so that vaccination with a live pathogen, even though it is weakened, carries a finite risk of causing a fatal infection. *Genetic engineering* (also known as *recombinant technology*) makes it possible to have single proteins of the pathogen produced in non-pathogenic microorganisms; injection of a person with these organisms stimulates antibody production against the foreign protein and therefore provides protection against the disease. The obvious advantage of this approach is the enhanced safety of the vaccine, since the single foreign protein cannot cause the disease. Recombinant vaccines made with only part of the genome of a pathogen are also known as subunit vaccines.

Recombinant vaccines may also prove to be cheaper than traditional vaccines because of innovative production

methods and, in some cases, because improved storage characteristics may not require them to be refrigerated. Much progress is being made in recombinant vaccine development. A major roadblock is the long time it takes for clinical trials and regulatory approval. To date, the number of products on the market is quite limited. Researchers are currently working to develop techniques to overcome some of the other difficulties too, for example, correct presentation of recombinant antigens to the immune system and the limited lifetime of the engineered protein in the body. Several types of recombinant vaccines exist, of which some are described below (Box 2.6).

BOX 2.6 TYPES OF RECOMBINANT VACCINES

Viral vector vaccines consist of a benign virus that has been genetically modified to contain genetic material belonging to the pathogen. After the vaccine has been injected, the virus attaches to the individual's cells and injects its genetic material into the cell's interior. The foreign genetic material gets incorporated into the cell's genome. The cell follows the genetic code and manufactures the antigens of interest, which trigger the immune system into producing a protective immune response.

Naked DNA vaccines, or plasmid DNA vaccines as they are also known, are very similar to viral vector vaccines. The key difference is that naked DNA vaccines use a different biological carrier, known as a plasmid, to introduce the antigen genes into the individual's cells. Plasmids are small circular molecules of DNA that are normally found in bacteria. They can easily enter cells and recruit the cell to translate their genetic information into protein. Advocates of this approach argue that developing naked DNA vaccines is potentially faster, cheaper and easier than other types of vaccines and, because DNA is heat-stable, these vaccines are able to bypass the cold chain, a major cost barrier to efficient vaccine delivery.

Plant-derived vaccines are subunit vaccines synthesized by plants. Plants typically used are those that are easily engineered to express foreign proteins, such as the tomato or potato. After introducing the pathogen genes into the plant's DNA, the plant is given a signal to make the protein in its tissues. The antigens expressed by the plant are purified and can then be used as vaccines. In essence, the plants act as vaccine-factories. There are several advantages to plant-derived vaccines. They can be relatively inexpensive to produce, store, and transport and they could be grown locally, making them attractive for applications in developing countries.[58] Researchers are making significant progress in the development of plant-derived vaccines. In comparison to the existing hepatitis B vaccine, a potato-derived vaccine was found to produce greater immunity in mice.[59] Plant-derived vaccines are also being developed for several important causes of infant mortality, including infant diarrhea and measles.[60 a, b, c]

The examples below illustrate current advances of recombinant vaccine technology for various diseases.

BOX 2.7 RECOMBINANT VACCINES IN DEVELOPMENT

Most HIV vaccines currently in clinical trials are recombinant vaccines.[61] Currently there are 28 ongoing trials collectively involving 24 different vaccines. Of these, 8 are DNA-based, 8 use recombinant viral vectors, 5 are protein subunits and 3 are lipopeptides.[62] An HIV viral vector vaccine based upon the gp120 antigen[63] has shown encouraging results in a Phase II clinical trial with healthy volunteers.[64] Just over half of all volunteers generated antibodies that neutralized HIV-1. When received in combination with an injection of gp120, the proportion rose to 94%. Phase III trials began in late 2003. In recent trials on Rhesus macaques, researchers assessed the protection conferred by recombinant forms of HIV gp120, a fusion protein constructed from HIV regulatory proteins Nef

and Tat, and SIV Nef. Treatment with this recombinant multi-antigen vaccine delayed the onset of AIDS in Rhesus monkeys for at least 2.5 years following infection with a simian-human hybrid virus (S-HIV).[65]

The much-awaited initial results of a three-year multi-ethnic phase III trial of AIDSVAX by researchers at VaxGen Inc. have been disappointing.[66] Produced in mammalian cell culture, AIDSVAX is a recombinant form of gp120. It is non-infectious and mimics proteins on the surface of two strains of HIV subtype B (prevalent in North America, Europe, Australia, Japan and Puerto Rico). The FDA would have considered approving the vaccine if it were 30% effective, but the reduction of infection among the entire sample of volunteers including all racial groups was only 3.8 %. The study did not show a statistically significant reduction of HIV infection within the study population as a whole, which was the primary endpoint of trial. Nonetheless, larger and statistically significant reductions were observed in some ethnic groups, especially among African-Americans, so further studies on this vaccine are warranted.

A naked DNA vaccine against HIV / AIDS is currently being evaluated in The Gambia and England, with good results. The first multi-clad HIV vaccine to enter clinical trials is also a naked DNA vaccine.[67] By preventing infection by the three most important subtypes of the virus around the world, it is hoped that this vaccine would be effective in both developing and developed countries.

All said and done, however, the progress of HIV vaccine development has been slow and disappointing.[68] After 10 years of work in this area, scientists now believe that live, attenuated vaccines may be more appropriate for the fast-evolving and diverse HIV.

The story of recombinant vaccines against malaria is more promising. A subunit vaccine known as RTS,S / AS02 was recently shown to provide protection against natural malaria infection in adults in a clinical trial in the Gambia, with 71% of the participants protected from infection for the first 9 weeks of the study.[69] Clinical trials on children in both The Gambia and Mozambique are now underway.[70] Another subunit vaccine protected four of five monkeys from a lethal injection of malaria.[71] This particular vaccine is synthesized by mice and excreted in their milk. The developers have expressed interest in creating transgenic goats for large-scale production.

Tuberculosis claims at least 2 million lives every year. Researchers are actively working towards a potent TB vaccine.[72] Progress to date includes a subunit vaccine based upon the Mtb8.4 surface antigen that protected mice from virulent TB infection.[73]

Hepatitis B affects approximately one third of the world's population and is associated with liver cancer. Tomatoes and lettuce have been genetically engineered to produce hepatitis B surface antigens, and these appear to induce an immune reaction similar to hepatitis B proteins isolated from infected humans.[74]

Scientists are developing plant-derived vaccines against the major causes of infant diarrhea. For instance, researchers successfully produced a strain of corn that expresses an antigen associated with enterotoxic *E. coli*.[75] Mice that were fed the corn exhibited elevated levels of antibodies in their blood, and showed resistance to infection. Also, the gene for the highly antigenic, but non-toxic, beta chain of the cholera toxin has been expressed in alfalfa, and mice fed with this alfalfa showed an immune response against cholera toxin. However, it will probably take many years of careful experimentation before such vaccines are approved for human use.

3. VACCINE & DRUG DELIVERY

- Reduce child mortality
- Combat HIV / AIDS, malaria and other diseases

Closely related to advances in vaccines are improved methods of vaccine and drug delivery. Consequently, these new technologies will also serve to meet the fourth, fifth and sixth Millennium Development Goals as mentioned in the previous section, ***Reduce child mortality***, ***Improve maternal health*** and ***Combat HIV/AIDS, malaria and other diseases***. Thousands of children die each year from vaccine-preventable diseases because the logistics of vaccine delivery are prohibitively expensive. Refrigerated transport and storage ("the cold chain") is a major expense in all vaccine programs. Another factor that raises costs is trained medical personnel who can deliver vaccinations. Unsanitary drug and vaccine injections are associated with the spread of blood-borne diseases among the population, particularly HIV and hepatitis. It is estimated that reuse of needles causes 80,000 to 160,000 new cases of HIV/ AIDS, 8 to 16 million new cases of hepatitis B and 2 to 4 million new cases of hepatitis C each year.[76] Long and complicated drug regimens are difficult for people to comply with, especially if they involve visits to medical facilities. When patients fail to complete their treatments, they not only fail to recover, but partial treatment can lead to the emergence of drug resistant strains of disease.[77]

Injection-free and controlled-release delivery systems could help to solve many of these problems. The scientific community is exploring a number of alternatives to needle-based delivery of drugs or vaccines. The skin, for instance, is an attractive route into the body because of its easy access. Needle-free injections propel the vaccine or drug through the skin and into the body with a high-speed jet of gas. Solutions, rubbing gels and skin patches rely on simple diffusion to introduce agents into the body. Another avenue into the body is the mucus membrane that lines all of the inner cavities of the body, including the intestines and the lungs. Mucus membranes are abundant and are closely associated with the bloodstream (which is important for drug absorption). Vaccination in the lung membranes generates immunity in the rest of the body's mucus membranes in addition to the systemic immunity generally conferred by vaccines. Consequently, the introduction of drugs and vaccines across the respiratory tract through nasal sprays and inhalers is an attractive option.

As mentioned earlier, the refrigeration required for storing and transporting conventional vaccines and drugs is costly. The discovery that some microorganisms can be rejuvenated after complete dehydration has led to the exciting development of powdered vaccines and drugs that are heat-stable. These organisms contain a non-reactive sugar (trehalose) that stabilizes them while they are desiccated. With this and other stable sugars, researchers have been able to dehydrate liquid vaccines and drugs and store them at room temperature for up to several months without affecting their potency. Associated injection devices for dried vaccines have been developed. Some involve the reconstitution of the dried substance into a liquid just prior to injection, while others introduce the substance into the body through the skin as a powder using needles or a high-speed jet of gas.

Improved drug delivery can also help to reduce the length and complexity of drug treatment regimens. Controlled-release drugs and vaccines can be introduced into the body in association with a biodegradable polymer that gradually releases its contents as it is broken down by the body. One disease for which this would be very useful is tuberculosis, which has risen to epidemic levels. Sustained-release antibiotic treatments, which automatically release their contents overtime, would lower the number of doses a patient must receive, thereby increasing compliance and limiting the emergence of drug resistant strains of TB. Preliminary studies of controlled release antibiotics have been promising.[78] Recently a group has reported the development of temperature-stable, controlled-release formulations using oligosaccharide ester derivatives of trehalose and a synthetic peptide analogue of hepatitis B surface antigen.[79] The ability of these novel delivery systems to induce strong immune responses in

mice without the requirement for multiple doses or cold-chain storage is encouraging.

BOX 2.8 INJECTION-FREE DELIVERY SYSTEMS

Advances in needle-free vaccine delivery include inhalable formulations, skin patches and powdered vaccines.

Inhalable - An inhalable form of insulin is in the late stages of development, and promises to reduce the risks, discomfort and inconvenience associated with daily insulin injections.[80] Between 1988 and 1990, close to 4 million children in Mexico were immunized against measles using an inhalable vaccine.[81] Those involved in the campaign noted that the approach was cheaper, faster and more widely accepted than the traditional method of giving injections.

Skin Patch - A skin patch system that uses a benign virus to carry vaccinating genes across the skin is under development and has performed well in animal studies against influenza, tetanus and rabies.[82]

Powdered - Powdered vaccines against yellow fever and tuberculosis are already available, although the expense of the associated injection devices will have to be carefully assessed.[83]

4. BIOREMEDIATION

- Combat HIV / AIDS, malaria and other diseases
- Ensure environmental sustainability

Technologies for environmental improvement (sanitation, clean water, bioremediation) were ranked fourth in the list of technologies to improve health in developing countries. Bioremediation has direct significance to the seventh MDG, ***Ensure environmental sustainability*** but it also has impact on the health-related goals.

Bioremediation is the use of bacteria or plants to clean up the environment. Reduction of pollution in water supplies and in the food chain will help to reduce mortality and improve health. There are two main types of pollution threatening the health and well-being of human populations: organic waste and heavy metals such as lead, mercury and cadmium. Bacteria can detoxify both. Plants can break down most forms of organic waste, but, with very few exceptions, are usually unable to metabolize heavy metals. On the other hand they can store harmful metals in their tissues and therefore make it easier to collect, harvest and even recycle metal waste.

Water contaminated by human waste harbors large amounts of pathogenic organisms and has been implicated in the transmission of cholera, typhoid, hepatitis A and other waterborne diseases. Sewage treatment can dramatically reduce the incidence of these diseases. Bioremediation techniques can augment conventional chemical sewage treatment. A number of low-cost alternatives to conventional sewage treatment have been developed. One such system is now in use in Southern China. It uses floating rafts called Restorers to supply beneficial microorganisms to a canal contaminated with human waste.[84] In fact, this floating ecological treatment engine has now been transformed into a garden featuring over 10 species of native Chinese wetland plants.

Bioremediation can also be used to reduce environmental pollution associated with heavy industries, including oil spills, acid mine drainage, and radioactive waste. In 1989 the tanker Exxon Valdez released 11 million gallons of oil off the coast of Alaska, affecting approximately 2000 km of shoreline.[85] Through the addition of extra nutrients to the beach, crews were able to enhance local bacterial and algal populations and take advantage of their ability to degrade petroleum.[86]

Acid mine drainage is associated with the leakage of contaminated water from mining sites. The drainage is toxic for both humans and the surrounding environment. Constructed wetlands are a common low-cost, sustainable

solution to this problem.[87] The area is artificially saturated with water, plant species are introduced, and these eventually lower the acidity and the metal concentrations at the site.

The bacterium *Deinococcus radiodurans* has the ability to thrive in environments with 300 times the fatal dose of radiation for humans. Researchers have genetically engineered *D. radiodurans* to express several genes associated with mercury detoxification. The recombinant bacterium has been shown to metabolize mercury while being bombarded by high levels of radiation, suggesting that bioremediation may be able to aid in the process of radioactive waste cleanup.[88]

Bioremediation can also help to clean up mosquito-infested water and control the spread of malaria. For example, the malaria-carrying *Anopheles* mosquito has developed resistance to chemical insecticides. Many anti-malarial prophylactics that were once effective are now less reliable, not to mention expensive for many people in developing countries. Peru has one of the highest rates of malaria in all of Latin America. Canada's International Development Research Centre (IDRC) has supported research at the Instituto de Medicina Tropical "Alexander Von Humboldt" in Lima to explore the use of coconuts in the fight against malaria. Researchers at the Institute have developed an ingenious method to biologically control mosquitoes that is simple, inexpensive, and an environmentally safe alternative to insecticides. It involves the use of coconuts used to culture bacteria that are toxic to mosquito larvae but harmless to people and other organisms. *Bacillus thuringiensis* var. *israelensis* H-14 (*Bti*) is a spore-forming bacterium that produces a toxin lethal to mosquito larvae. Imported *Bti* cultures are expensive, but as this project shows *Bti* can be cultured locally and cheaply using coconuts, which are both cheap and plentiful in many tropical areas. *Bti* is introduced via cotton swabs into the coconut and allowed to incubate inside the coconut for a few days. The nut is then broken and tossed into ponds where mosquitoes breed. The mosquito larvae eat the bacteria and are killed. A typical pond needs only two or three coconuts for each treatment – usually lasting 2 months.[89]

BOX 2.9 BIOREMEDIATION TO THE RESCUE: ARSENIC POISONING IN BANGLADESH

Bangladesh is currently facing "the largest mass poisoning of a population in history" due to naturally-occurring groundwater arsenic contamination.[90] At least 100,000 cases of debilitating skin lesions are believed to have already occurred because of the seepage of arsenic into the water supply, and at least 50 million people are at risk. Recently discovered in a gold mine in Australia, a bacterium named NT-26 may be able to help.[91] NT-26 has the natural ability to transform arsenite, a soluble form of arsenic, into the much less toxic form arsenate. The Australian Research Council is supporting research to investigate the potential of NT-26 to reduce the toxicity of arsenic dissolved in water. Knowledge of the genomic sequence of NT-26 and other arsenic metabolizing bacterial species could help to enhance bioremediation tools to decontaminate the wells. Genome Canada has recently announced that it will sequence the genomes of two arsenic-metabolizing bacteria, including NT-26. This move is part of a greater Canadian initiative to harness Canadian R&D for global health.

Researchers at the University of Florida have discovered that the brake fern *Pteris vittata*, has a remarkable ability to accumulate arsenic in extremely high concentrations without any apparent harm to itself.[92] The unusually sun-loving fern could be cultivated in arsenic-contaminated water and act as a natural arsenic filter. The fern collects the arsenic in its fronds, which are easy to harvest, although scientists admit that more work is needed on how to dispose of the plants. Further research is also looking into identifying and then splicing the fern's arsenic-metabolizing genes into other plants.

5. SEQUENCING PATHOGEN GENOMES

- Combat HIV / AIDS, malaria and other diseases

The sequencing of pathogen genomes has direct relevance to the fourth Millennium Development Goal, ***Combat HIV/AIDS, malaria and other diseases***.

The task force for this MDG has prepared documents on HIV/AIDS, malaria and TB that take an in-depth look at the science, public health needs and medical interventions, and the social and economic issues and consequences of these devastating diseases. Pathogen genomics can also contribute to the search for a solution of these diseases.

Sequencing a genome involves discovering and recording the entire sequence of nucleotides in an organism's DNA. DNA codes for proteins, which are the mainstay of structure and biochemical function in all organisms. Knowing the sequence of a pathogen's genome is therefore helpful in unraveling its biology and discovering effective ways of controlling its relationship with humans.

Most sequencing strategies are based upon a technique known as the dideoxy or Sanger method.[93] Small-scale sequencing projects can be done manually, but large-scale projects (such as the sequencing of an entire genome) require high-throughput automated DNA sequencing machines. Major sequencing projects use many automated sequencing machines simultaneously, yielding millions of bases of sequence data per day. These data must be stored, managed and analyzed by computers and this requirement has given rise to an entirely new field in biology - bioinformatics.

Knowing the sequence of a pathogen's genome can rapidly accelerate the process of drug discovery. Comparative genomics is a method that compares the genomes of different organisms in order to apply information known about one organism to another. For example, in a comparison of disease-causing and benign strains of the same organism, genes unique to the pathogenic strain are likely to play an important role in pathogenesis, and the proteins for which they code may make excellent drug targets.[94] Alternatively, if one pathogen has a gene that is a known drug target, a comparative genomics search might reveal a similar gene, and therefore a potential drug target, in another pathogen.

BOX 2.10 THE RESURRECTION OF FOSMIDOMYCIN

Genomics and bioinformatics, in the hands of innovative researchers, resurrected the little-used drug fosmidomycin off the shelf and brought it into clinical trials as a novel anti-malarial drug in less than two years.[95] The team successfully searched the *Plasmodium falciparum* genome for the gene of an enzyme targeted by fosmidomycin, an antibiotic developed and manufactured by a Japanese pharmaceutical company. In vitro studies have indicated that fosmidomycin inhibits the growth of multi-resistant strains of *P. falciparum*. When administered to adults in Gabon with malaria, fosmidomycin was found to be a safe and effective method of treatment.[96] The sequencing of the genome of *Anopheles gambiae*, [97] one of the mosquitoes that transmits the malaria parasite, could also open up new opportunities for controlling malaria, such as (1) identifying new targets for insecticide development; (2) strengthening our understanding of the developmental biology of mosquitoes; and (3) possibly controlling pathogen transmission.[98]

A serious health concern worldwide is the emergence of pathogen resistance to previously effective drugs. Analysis of pathogen genomes could reveal the genes that play a role in helping these organisms develop drug resistance and point researchers in the direction of treatments that can overcome the action of these genes. For example, scientists can compare the genomes of resistant and nonresistant strains, or analyze the genes at work in the drug resistant stage of an organism's lifecycle.[99]

In addition to spurring novel drug discovery, pathogen genomics has also given a boost to the development of vaccines. Researchers can search the genome of infectious organisms for gene sequences characteristic of antigens. For example, scientists have discovered vaccine candidates for a particularly virulent strain of meningitis, a potentially fatal bacterial infection. Of the 570 antigens found, 85 showed promise when used to immunize mice.[100]

6. FEMALE-CONTROLLED PROTECTION AGAINST SEXUALLY TRANSMITTED INFECTIONS (STIS)

- Promote gender equality and empower women
- Improve maternal health
- Reduce child mortality

Genomics and other biotechnologies are enabling the development of a number of new forms of female-controlled protection against STIs, such as recombinant vaccines, monoclonal antibodies and new approaches to the development of vaginal microbicides. These technologies can help to meet the sixth MDG ***Combat HIV/AIDS, malaria and other diseases*** and even the third MDG, ***Promote gender equality and empower women*** with an indirect effect on other health MDGs: e.g. ***Reducing child mortality*** by ***Improving maternal health***.

The global burden of STIs is felt most heavily by women. A decade ago, the World Bank ranked STIs as the second major cause of ill health among women aged 15 to 44, accounting for 8.9% of their disease burden, compared to 1.5% in men.[101] For various reasons – socio-economic, cultural and biological – women are more vulnerable to infection than men.[102] Women with STIs often bear heavy social stigma, and they often have neither the time nor the money to seek health care. Rising infection in women also increases the incidence of transmission from mother to newborn.

Despite the seriousness of this problem, women possess few means of protection. The condom requires male consent, which many women living in patriarchal societies find hard to negotiate in their relationships. Although the female condom has been greeted with enthusiasm by women in poor countries, its cost and indiscreetness make it a less than ideal option. Vaginal microbicides are one attractive alternative. They are gel or cream formulations of chemical compounds that block the transmission of infection across the vaginal wall. Researchers are actively involved in developing safe and effective vaginal microbicides.

BOX 2.11 NONOXYNOL-9

The spermicide nonoxynol-9 (N-9) appeared to be very promising, but rigorous clinical trials have demonstrated that N-9 may in fact increase a woman's susceptibility to infection through its effect on the vaginal wall.[103] Researchers are currently looking for more effective spermicides.

Initial approval for nonoxynol-9 (N-9) was as a contraceptive, but early laboratory tests suggested that it might be an effective microbicide. However, it is now clear that N-9 does not protect against HIV infection and may in fact increase the risk of infection in women who use it frequently. N-9 is a cytotoxic compound. In addition to killing microbial cells, it also harms the cells that line the vagina and cervix. Studies have shown that at high doses, N-9 can destroy the vaginal wall lining, and a WHO/CONRAD study has concluded that, when used alone, N-9 is only moderately effective in preventing pregnancy.

Nonetheless, N-9 spermicides do have some useful characteristics – they are readily available, and are female-controlled. Therefore, while the N-9 clinical trials have proved disappointing, they do show that similar but less toxic spermicides may be an effective weapon against the spread of STIs.

SOURCE: World Health Organization.

Externally applied antibodies have shown significant promise in blocking STI transmission. In studies involving humans or animals, monoclonal antibodies have been shown to provide protection against HIV, Herpes Simplex Virus 1 and 2, Hepatitis A and B and chlamydia.[104]

A number of other types of vaginal microbicides are in development. One product, Carraguard, is made from the natural seaweed compound carageenan. Carageenan is already widely used as a food thickener and cream emulsifier. Phase I studies have shown that Carraguard is well-tolerated. Phase I and II trials have been completed, and phase III trials are due to start in 2004.[105]

The National Institute of Allergy and Infectious Diseases (NIAID) of the United States has focused on two microbicides: BufferGel, which acts by maintaining the normal acidity of the vagina, and PRO2000, which inhibits viral entry into cells. Phase I trials of both products have shown them to be relatively safe and well-tolerated.[106] Phase II/III data on BufferGel's contraceptive activity are expected in 2004; data on the anti-HIV activity of BufferGel™ are expected in 2006.

Recently, the Bill & Melinda Gates Foundation granted $60 million to the International Partnership for Microbicides (IPM) to accelerate the discovery, development, and accessibility of topical microbicides to prevent HIV transmission. This grant is the largest ever made to support microbicide research. IPM also received a grant of $15 million from the Rockefeller Foundation. This program is expected to deliver a safe and effective product by the end of this decade.

A novel polymer has been shown to block the binding of HIV and herpes simplex to cells by targeting the surface antigens gp120 and gB-2 respectively. It is highly selective and exhibits low cytotoxicity[107], the latter a considerable advantage over existing vaginal microbicides.

Lactobacillus, a bacterium that normally inhabits the vagina, is another potential alternative to synthetic microbicides. It could protect women against STIs in two ways. First, the bacterium naturally produces hydrogen peroxide, which kills infectious organisms. Second, the bacteria could be genetically engineered to synthesize a compound called CV-N.[108] CV-N has been shown to bind to and inhibit all known strains of HIV. It was only recently discovered by researchers at the National Cancer Institute of the United States in the blue-green algae *Nostoc ellipsosporum*.[109] Since *Lactobacillus* normally inhabits the vagina, and CV-N has been found to not irritate the vagina, researchers are hopeful that this genetically modified organism may function as a safe and affordable vaginal microbicide. Research suggests that even in an unmodified form, the bacterium *Lactobacillus jensenii*, which lives in the mucosal linings of the vagina, provides some protection against infection with HIV because women with low amounts of the microorganism are believed to be at relatively higher risk of contracting sexually transmitted infections. Recently, investigators at Stanford University have modified *Lactobacillus jensenii* to secrete CD4 proteins to inhibit HIV.[110] In the process of infection, HIV attaches itself to the CD4 molecule on immune cells. Genetically modified lactobacillus was shown in laboratory tests to reduce by half the number of immune cells infected by HIV. This is a promising finding that may lead to the development of a discreet vaginal suppository that women could use for protection against infection with HIV.

Perhaps the ideal method of female-controlled protection against STIs is vaccination. Vaccines afford extended, often life-long protection. Vaccines also have no impact on the sexual encounter and do not entail a contraceptive effect, unlike, for example, the condom. Hepatitis B, the only STI for which a vaccine exists, is a subunit vaccine that is synthesized by the common yeast *Saccharomyces cerevisiae*. Subunit vaccines are currently being developed against numerous STIs, including human papilloma virus (HPV), chlamydia, gonorrhea and hepatitis C.[111, 112]

7. BIOINFORMATICS

- Combat HIV/AIDS, malaria and other diseases

As mentioned earlier, bioinformatics is a new tool that goes hand-in-hand with genomics, and therefore has important applications to ***Combat HIV/AIDS, malaria and other diseases***.

Bioinformatics is the application of computer hardware and software to store, retrieve and analyze large quantities of biological data. The so-called "high throughput" technologies (DNA sequencers, DNA and RNA microarrays, combinatorial chemistry, 2D gel electrophoresis and mass spectrometry) have resulted in an explosion in the amount of biological data available. Bioinformatics organizes this sea of biological data into meaningful databases and conducts sophisticated computer analyses ("data-mining") to generate answers to research questions. Its importance to the field of biotechnology is reflected in its seventh ranking among the most promising biotechnologies for improving health in developing countries within the next five to ten years. Bioinformatics is an indispensable partner for genomics, and together these two technologies are poised to revolutionize the way we approach drug and vaccine discovery.

Biological databases are central to bioinformatics, and several have been established as public resources available to all via the Internet (Box 2.12).

BOX 2.12 BIOINFORMATICS DATABASES

Large sequencing projects require the resources of large organizations. Fortunately, much of these resources, as well as the data they generate, are shared. GenBank is a massive online database of all publicly available gene sequencing that can be accessed free of charge over the Internet.[113] GenBank is maintained by the National Center for Biotechnology Information (NCBI) of the National Institutes of Health (NIH) of the United States. As of October 2003, there were over 33 billion base pairs of sequence data in GenBank. GenBank exchanges data with the DNA DataBank of Japan (DDBJ) and the European Molecular Biology Laboratory (EMBL) on a daily basis.

SWISS-PROT is a protein sequence database developed by groups at the Swiss Institute of Bioinformatics (SIB) and the European Bioinformatics Institute (EBI).[114]

The Molecular Modeling Database (MMDB), also maintained by the NCBI, contains 3D biomolecular structures, including information on biological function and the evolutionary history of large molecules.[115]

AnoDB is a database containing genomic and biological data on anopheline mosquitoes, in particular *Anopheles gambiae*, one of the most important vectors of malaria.[116]

Bioinformatics applies computer algorithms to transform large-scale biological data into useful information. For example, an algorithm could be applied to quickly identify specific families of genes in the recently-sequenced genome of *Anopheles gambiae*. Without bioinformatics, this task would be extremely laborious and error-prone, and it would take scientists several years to realize the potential of this genome sequence. Many bioinformatics algorithms are shared worldwide and available free over the Internet along with basic tutorials. They can generally be found on the websites of public bioinformatics databases. Their accessibility to scientists helps to promote R&D. To help meet the worldwide demand for skilled bioinformaticians, a consortium of six universities is offering a free accredited web-based course in bioinformatics.[117]

One of the key applications of bioinformatics to diseases is the accelerated discovery of drug targets. A drug target is a biological molecule, most commonly a protein, with which a drug interacts to alter its function. Most drug tar-

gets fall into one of only a few categories, such as cell surface receptors, enzymes or ion channels. (A drug may work, for example, by interacting with, and inhibiting, a pathogen-derived enzyme that causes disease in humans). Searching the genome of a pathogen or vector for sequences that are characteristic of genes that encode these types of biological molecules can lead to the identification of drug targets. Comparative genomics, in which the genomes of several organisms are analyzed in relation to one another, can also be used to identify drug targets.[118] By comparing the genome of a pathogen with that of one of its close yet harmless relatives, researchers can identify genes that are unique to the pathogen. These genes may play a role in the development of disease, and a drug that affects the proteins that correspond to these genes may be able to disrupt the pathogen's ability to cause disease. Comparative genomics can also serve to identify genes that share similar sequences between different strains of a virus. Such stable (relatively non-mutating) genes may make effective, long-lasting, and multi-strain drug targets because they are likely to be necessary for the organism's survival, have not demonstrated a tendency to mutate, and are shared across strains.[119] Bioinformatics has made all these approaches much easier and less time-consuming.

Besides identification of drug targets, bioinformatics can also play an important role in drug *design*. The rational design of a drug that interacts with the target appropriately and effectively calls for information on the three dimensional structure of the target molecule. Researchers can learn about the 3-D structure of a novel target by conducting amino acid sequence similarity searches among proteins of known structure. By comparing the amino acid sequence of a protein of known structure to that of the potential drug target, researchers can make predictions about the structure of the target and embark upon the design of the drug in an intelligent fashion. Structure-based design is one of the most successful ways of creating drugs.[120]

Similarly, bioinformatics can be used for the discovery of vaccine candidates. A vaccine candidate is a molecule that shows promise as a vaccine. Vaccines typically contain antigens that stimulate the immune system to generate a protective response against infection. Most antigens are proteins found on the surface of the pathogen, and the genes that encode these proteins have characteristic sequences. By searching the genome of a pathogen for these sequences, researchers have been able to identify several new vaccine candidates. In their analysis of *Chlamydia pneumoniae*, a cause of respiratory infections, researchers identified 147 cell surface proteins.[121] Of these, 58 produced an immune response when injected into mice. In this case, bioinformatics techniques have clearly helped researchers understand and tackle an organism that has been a challenge to study using conventional laboratory techniques.

Bioinformatics can also supply useful information on drug toxicity and side-effects. Searching the human genome for a gene sequence similar to that of a drug target can give researchers a clue as to whether or not this drug will also interact with proteins other than the target and therefore have undesirable side effects.[122]

8. NUTRITIONALLY ENRICHED GENETICALLY MODIFIED CROPS

- Reduce child mortality
- Improve maternal health
- Combat HIV / AIDS, malaria and other diseases

Nutritionally enriched GM crops are germane to the three health-related Millennium Development Goals, ***Reduce child mortality, Improve maternal health*** and ***Combat HIV/AIDS, malaria and other diseases.*** Over half of all infant deaths in developing nations are associated with a lack of essential vitamins and nutrients. Malnutrition also causes impaired cognitive and physical development, and is associ-

ated with multiple illnesses attributed to specific nutrient deficiencies. These include blindness due to Vitamin A deficiency, which affects an estimated 500,000 children in developing countries.[123] Anemia is caused by iron deficiency and is one of the leading causes of maternal mortality.[36] Pregnant women with anemia are more likely to give birth to low birth weight infants and are at increased risks of death during childbirth. Malnutrition, which affects approximately one in five people living in developing countries, amplifies the effects of infectious diseases. Lack of essential vitamins and minerals impairs the immune system, thereby increasing the likelihood that infection will develop into disease and impairing the ability of the body to recover.

Genetically modified crops are those whose composition has been altered by genetic recombination. This involves the insertion of a gene – either with a gene gun or a carrier organism such as a benign virus – into a plant very early on during development such that all of the plant's cells acquire the gene. Various traits can be introduced into crops through genetic modification. One application of genetic modification in crops is to enhance the nutritional value of crops. This type of modification might involve, for example, the insertion of genes that encode for enzymes that synthesize vitamins. The Top 10 study ranked nutritionally enriched GM crops eighth among the most promising biotechnologies for improving health in developing countries in the next five to ten years.

The potential advantages of nutritionally-enhanced crops for developing countries are difficult to deny. More than three million children under five suffer eye damage because of Vitamin A deficiency. About 500,000 go blind every year, of whom two-thirds die. Many are children of small farmers or farm workers too poor to afford a highly diversified diet. Some experts maintain that the one effective way of combating their Vitamin A deficiency is to increase the Vitamin A content of their staple food. Accordingly, Ingo Potrykus and fellow researchers at the Swiss Federal Institute of Technology and the University of Freiburg in Germany developed rice enriched in ß-carotene, known as "Golden Rice". With grants from Rockefeller Foundation and Swiss funding sources, they worked on this project for eight years, inserting seven genes in all, and establishing for the first time the feasibility of genetic modification involving multiple genes. Golden Rice stands apart as a model example of the use of gene technology to enhance the nutritional value of a staple food crop.[124] Golden Rice contains elevated levels of pro-Vitamin A (ß-carotene) and iron.[125]

BOX 2.13 GOLDEN RICE: IMAGINATIVE USE OF INTELLECTUAL PROPERTY RIGHTS

It was the original intention of the inventors of Golden Rice to offer their invention free of charge to poor farmers. All 32 companies holding the 72 patents that were used in the making of Golden Rice agreed to relax their patent rights. Commercial rights were assigned to Syngenta, the largest agribusiness in the world, and Syngenta agreed to allow subsistence farmers to use the rice without charge as long as they earn no more than $10,000 from the sale of the rice.[126] A humanitarian board composed of the two inventors and representatives of the Rockefeller Foundation, WHO and the biotechnology industry is overseeing the transfer of this technology to the developing world. In February 2001, the first delivery of Golden Rice was made to the International Rice Research Institute (IRRI) in Los Baños, Philippines.[127] Other deliveries are planned to non-commercial research institutions in China, India, Africa and Latin America. These research institutions will cross Golden Rice with locally adapted strains and conduct tests to ensure that the rice has nutritional value and is safe for consumption and the environment. They will also conduct need assessments, analyze alternative ways to address these needs, and establish a framework for the best use of Golden Rice. If Golden Rice is demonstrated to be a safe and substantial source of vitamin A and iron, it will enable affordable, sustainable, widespread nutrient supplementation in areas of the world that need it most.

Golden Rice contains elevated levels of pro-vitamin A and iron. (Courtesy of Peter Beyer, University of Freiburg, Germany)

More recently, researchers in India have developed a potato rich in all essential amino acids.[128] This potato contains the gene AmA1 that codes for the protein albumin, which contains high levels of all amino acids that the body is incapable of making on its own (i.e. essential amino-acids). It gives ordinary potatoes a third more protein than normal, including substantial amounts of the essential amino acids lysine and methionine. Deficiency in these can have an adverse effect on development in children. This enriched potato is also particularly relevant for India, where a large percentage of the population is vegetarian.[129] The AmA1 gene was obtained from the amaranth plant which grows in South America. The potato is in the final stages of testing, and it has been submitted for official approval. Scientists say that the protein-rich genetically modified "protato" could help combat malnutrition among the country's poorest children.

Researchers have also inserted into lettuce the gene for the enzyme GLOase, which converts a precursor molecule into Vitamin C.[130] They observed up to a seven-fold increase for Vitamin C in the plant's tissues. Vitamin C is a powerful antioxidant and is associated with reduced risks of cancer, cardiovascular disease and other diseases.[131]

Genetic modification and traditional breeding both change the characteristics of an organism, but in different ways. In traditional breeding, the introduction of a gene into an organism by cross breeding different strains of the same species is a trial-and-error process that takes a long time. Genetic modification makes it possible to introduce new genes more rapidly and more precisely than traditional breeding and enables the introduction of new genes from different species. In many cases, traditional breeding alone is able to improve the nutritional value of a crop. In fact farmers have used traditional breeding over thousands of years to convert the wild, almost inedible forms of rice and wheat into the familiar foods we eat today. However, genetic modification has the advantage of speed and relative control. This approach has its advantages and disadvantages. An obvious disadvantage is that that the introduced foreign genes may cause unknown gene-gene or gene-environment interactions. Ecological concerns include risks to human and animal health, food safety, and unforeseen consequences of the spreading of foreign genes into the natural environment. Gene-flow, the natural spread of genetic traits when a plant variety is introduced into the environment, is in itself not alarming, but the potential introduction of cross-species genes and the spread of these genes that confer novel traits upon related weeds or crops could be. However, it is important to note that all plant breeding, whether traditional or through genetic engineering, can produce unexpected results. Some scientists recommend that extensive testing and careful monitoring are necessary for the world to reap the benefits of this technology while avoiding any potential risks.[132] Others argue that all plant varieties, whether GM or not, should be subject to the same stringent standards.[133a, b] Although GM enriched crops are considered by many to be extremely important for health in developing countries, there are some concerns regarding their use. There is, for example, evidence that Golden Rice may not be a very good source of Vitamin A. Specifically, people with diarrheal diseases, which are common in the developing world, are unable to efficiently absorb Vitamin A from the rice. Critics also maintain that GM enriched crops are not the answer to the problems of hunger and malnutrition, which are the outcomes of distributional problems. Several organizations are actively researching these issues. The Food and Agriculture Organization of the United Nations and the World Health Organization jointly recommend the thorough evaluation of GM foods for safety and nutritional value before consumption or releasing the foods into the environment.

9. RECOMBINANT THERAPEUTIC PROTEINS

- Combat HIV / AIDS, malaria and other diseases

Therapeutic proteins, such as insulin, are used to treat many non-communicable diseases, and the technology to make

recombinant therapeutic proteins was ranked ninth among the most promising biotechnologies for improving health in developing countries within the next five to ten years. This technology is therefore significant for the sixth Millennium Development Goal, ***Combat HIV/AIDS, malaria and other diseases***. As poorer nations move through the process of development and associated demographic change, they face a double burden of disease: infectious diseases as well as non-communicable diseases more commonly associated with the developed world. In fact, non-communicable diseases (including injuries) now account for 60% of all deaths in developing countries, and current trends suggest this number will reach over 70% by 2020.[134] Affordable and sustainable sources of therapeutic proteins for treating these diseases are therefore critical.

Since all organisms possess the molecular machinery necessary to manufacture proteins, in principle they possess the ability to make any protein. All they would require are the genetic instructions to do so. Using recombinant technology, researchers can insert a gene or genes for a therapeutic protein into an organism. As the organism grows, it reads and translates the foreign gene as it does its own genes, and produces the therapeutic protein, which can be harvested for medical use.

Bacteria, particularly *Escherichia coli*, were the first organisms to be drafted for the production of large quantities of therapeutic proteins. *E. coli* is a natural resident of the human gut. Under the right conditions, the bacteria grow and divide rapidly, producing a new generation every 20 minutes. As they grow, they accumulate the recombinant protein in their interior fluids. Protein purification processes harvest the protein from the bacterial culture.

Bacteria have one main disadvantage as protein factories: they are extremely simple organisms. Unlike the cells of more complex organisms, bacterial cells lack the ability to make specific chemical modifications to the proteins after the proteins have been translated from the DNA code. Most human therapeutic proteins require these types of modifications. As more complex organisms, yeasts can carry out many forms of protein modification, and, like bacteria, they reproduce quickly, easily and with simple nutritional requirements. Because of its safety and familiarity, *S. cerevisiae* is the most popular yeast for making recombinant proteins.

Mammalian cells are a more attractive source of recombinant therapeutic proteins. They possess the ability to perform almost all the post-translational modifications that a protein might need in order to function properly. Unfortunately, mammalian cell cultures are more challenging to maintain and have a lower protein yield than bacteria or yeast. One way around these limitations is the use of transgenic animals to synthesize recombinant proteins. A transgenic animal is a genetically modified animal. These animals are engineered to secrete the protein in an easily-harvested body fluid, such as milk, urine or semen. To limit the secretion of the protein to a particular tissue, researchers link the gene of interest to another genetic element that promotes the expression of the gene only in the target tissue. It is estimated that the use of transgenic animals to synthesize recombinant therapeutic proteins would be four to five times cheaper than using mammalian cell cultures.[135]

Plants, particularly corn, have also been explored for their ability to function as recombinant protein factories. Plants offer many advantages over the use of animals to produce recombinant proteins. Like yeast, plants have the ability to perform many of the steps required to refine complex proteins. They can also be grown in large quantities at low cost. Using plants also minimizes certain ethical concerns related to animal experimentation and use, as well as risks associated with animal viruses and bacterial toxins. However, transgenic plant expression systems have a relatively low protein yield. Another disadvantage limiting the therapeutic value of the plant-derived product is the difference between plant and mammalian post-translational modifications. For instance, many human proteins are glycosylated – i.e. after the proteins

are produced they have special sugars attached to them to help them conduct their functions normally. Researchers are working to overcome this barrier by creating transgenic plants that can carry out protein glycosylation. These transgenic plants contain human genes that make enzymes that catalyze the attachment of sugar molecules to proteins. In one case, a group in the Netherlands genetically modified a tobacco plant and then crossed the modified tobacco plant with a plant engineered to manufacture a mouse antibody.[136] The resulting plantibody had a glycosylation pattern that more closely resembled a mammalian antibody than any plantibody produced to date. There clearly is a need for further fine-tuning of this process but the science is well on its way.

Some of the more significant recombinant therapeutic proteins that would be useful for developing country diseases include erythropoietin for the treatment of anemia, follicle stimulating hormone for the treatment of infertility, alpha interferon for the treatment of viral infections and leukemia, and insulin for the treatment of type I diabetes. Previously, all insulin was harvested from the pancreas of pigs and cattle. Pig and cattle insulin vary slightly from human insulin, so some diabetics develop an allergic reaction to this medication. Recombinant technology has made non-allergenic human insulin available in abundance using a sustainable method (see Box 2.14). The patent on recombinant human insulin expired in January 2003, opening the door for entrepreneurs in developing countries to manufacture the product locally and supply the public with the recombinant protein at a more accessible price.[137]

BOX 2.14 HUMAN RECOMBINANT INSULIN

In August of 2003, Wockhardt Limited launched India's first recombinant human insulin product, making Wockhardt just the fourth company in the world – and the first outside the US and Europe – to develop, manufacture and market this life-saving drug for the management of diabetes.

This move has also made India the first Asian country to develop this complex technology. Until now, 90 per cent of insulin in India has come from pigs or cows. The Indian government has been making efforts since the early 1970s to manufacture insulin. Unfortunately, these efforts have not successful. The Indian market for insulin is valued at around $52 million. India has the world's largest population of diabetics, with an estimated 30 million people suffering from the disease. According to the World Health Organization, this number will rise to 57 million by 2025. Globally, the WHO has estimated that by 2025, the number of people with diabetes worldwide will more than double from 140 million to 300 million. The two main advantages of recombinant insulin over animal-derived insulin are its chemical, biological and physical similarity to human insulin, and the low risk of transmitting animal pathogenic infections.

Wosulin, Wockhardt's recombinant human insulin brand, was approved by the regulatory authorities after it proved its efficacy and safety in clinical studies involving 350 diabetic patients.

Three companies, one in United States and two in Europe, today control the global market for human recombinant insulin valued at over $3 billion. Wockhardt's success allows it to potentially compete in this market.

SOURCE: http://www.rediff.com/money/2003/aug/04wockhardt.htm

BOX 2.15 A MAJOR BREAKTHROUGH FOR MALARIA: RECOMBINANT PATHWAY TO ARTEMISININ

The antimalarial drug artemisinin was originally extracted from the plant *Artemisia annua* (sweet wormwood) in 1972 at the Chinese Institute of Material Medicine. It is the active ingredient in "qinghao", a herbal infusion tea that has been used for

years to treat malaria and hemorrhoids and finds mention in a Chinese medical text dated 340 AD.

Although the drug has been found to be effective against malaria strains that are resistant to existing treatments, a major drawback is that it is produced only in small quantities in nature. Commercial production of artemisinin currently relies on its extraction and purification from plant material, the yields of which are low. This has made it too expensive for widespread use in developing countries – until recently. In a major breakthrough, a research group at University of California, Berkeley has genetically engineered *E. coli* to produce yeast and plant enzymes that perform quick and efficient synthesis of artemisinin.[138] The chemical precursor to artemisinin belongs to an extremely important family of plant chemicals known as isoprenoids that are precursors to several important drugs, commercial flavorings and fragrances. For instance, the cancer drug taxol is derived from an isoprenoid. Isoprenoids are currently expensive for the chemical industry to synthesize from scratch and nearly as expensive to extract from plant material. The technique described by these investigators for transplanting yeast and plant genes to construct an entirely new metabolic pathway inside bacteria could find broad application in the production of several types of isoprenoids.

10. COMBINATORIAL CHEMISTRY

- Combat HIV / AIDS, malaria and other diseases

Combinatorial chemistry has bearing on the health-related Millennium Development Goals, particularly ***Combat HIV/AIDS, malaria and other diseases***. There are many diseases prevalent in the developing world for which effective and affordable treatments are lacking. Some pathogens, such as those that cause malaria and tuberculosis, are acquiring resistance to the only treatments available. Child mortality is caused in large part by pneumonia, diarrhea and malaria, three diseases that are acquiring drug resistance.[37] Combinatorial chemistry can be used to provide new or more effective medications for these diseases. It may also promote enterprise by helping industries in developing countries become competitive and economically viable in the global market. The increase in efficiency also potentially decreases costs, wastes less material and creates fewer by-products – all of which serve to protect the environment.

Combinatorial methods are easily automated techniques for making many different kinds of chemical compounds. The resulting collection of compounds, known as a library, is biologically screened to select the compounds with the most therapeutic promise. Developed first in the early 1980s, combinatorial chemistry has become a mainstay of drug discovery and development in industrialized nations. In many cases, it replaces the much more costly and time-consuming one-compound-at-a-time method. The scientific panel ranked combinatorial chemistry as the tenth most promising biotechnology for improving health in developing countries within the next five to ten years.

Two features make combinatorial chemistry exceptionally efficient for drug discovery and development: first, it is amenable to automation with robots doing most of the preparation and screening of compounds. Second, it also makes it possible to prepare many unique compounds from fewer experiments. For example, suppose a chemist wanted to improve upon a drug by varying its basic structure. If this drug had three chemical parts, with each part potentially varied in three different ways, this would represent 3x3x3=27 unique chemical compounds in just six steps.

For instance, two new classes of drugs against leishmaniasis were discovered using a combinatorial process that produced over 150,000 different compounds.[139] Leishmaniasis is a potentially fatal disease that is estimated to affect 12 million people around the globe. Researchers also used combinatorial chemistry to focus in on a more potent version of vancomycin, an antibody of last resort against which many diseases are acquiring resistance.[140] The most successful compounds in the library outperformed

the most powerful antibiotics on the market. A third example involves a drug for the treatment of heart disease, which is on the rise in developing countries. Researchers produced approximately 250 versions of a promising drug, one of which was RWJ-53308, which completed Phase II clinical trials in 2000.[141]

The International Centre for Science and High Technology at the United Nations Industrial Development Organization is engaged in capacity-building and transfer of technology to developing countries, since competitive industrial capability relies on scientific expertise.[142] Within the field of Pure and Applied Chemistry, ICS is promoting capacity-building in combinatorial chemistry methods and technologies. ICS emphasizes the importance of combinatorial chemistry for the rapid and efficient development of new chemicals – pharmaceuticals, agro-chemicals, and new materials. The tools used by ICS to achieve transfer of know-how include organization of training events, distribution of information packages, networking and offering of fellowships for researchers to learn hands-on techniques, and other methods.

BOX 2.16 DRUGS FOR NEGLECTED DISEASES INITIATIVE

Médecins Sans Frontières (MSF) has committed $25 million over 5 years for a new initiative to develop drugs for diseases of the developing world that have largely been neglected by research institutions in the developed world. Examples are sleeping sickness, leishmaniasis, and Chagas disease. MSF plans to run the Drugs for Neglected Diseases Initiative (DNDi) like a virtual pharmaceutical company, relying on combinatorial chemistry to create portfolios for neglected diseases. It will use the experience and resources, both financial and human, of institutions and facilities worldwide, by creating a global network of researchers. For example, DNDi will draw upon the research capacity of the Indian Council of Medical Research (ICMR), the Kenya Medical Research Institute (KEMRI), the Oswaldo Cruz Foundation (Fiocruz) of Brazil, and other established research institutions from the South. DNDi will also rely on the public health systems in these countries for access to patients and to organize high-quality clinical trials. Researchers at the Clinical Research Centre at KEMRI are creating an African network for DNDi, with representatives from Ethiopia, Eritrea, Ghana, South Africa, and Sudan among other countries.

With combinatorial chemistry approaches, DNDi plans to have six or seven drugs registered and a balanced portfolio of eight in the pipeline by 2015. Some critics observe that the budget of $255 million over the first 12 years is unrealistic, compared with the usual pharmaceutical company estimates of $500 million per drug. DNDi partners feel that in-kind contributions from collaborators and governments will help to make up the difference. They also expect the resulting drugs to be manufactured at relatively low cost by companies in developing countries.

SOURCE: www.dndi.org

Summary

This exercise in technology-foresight shows how the top 10 genomics-related biotechnologies can contribute to improving health in developing countries within the next ten years and can make diverse and significant contributions to the effort to achieve the UN Millennium Development Goals. Through the provision of simpler and robust diagnostics, new vaccines, safer methods of vaccine and drug delivery, empowerment of women, methods of environmental remediation and other techniques, the benefits of modern technology can reach the developing world. The examples described here indicate how genomics can promote development and reduce poverty, both by improving health and by forming the basis of new industries in developing countries.

— CHAPTER THREE —

GENOMICS AND GLOBAL GOVERNANCE

In the previous chapters of this report we established that genomics and biotechnology represent important tools for addressing the Millennium Development Goals. Efforts to create a receptive environment for technological innovations and their application in developing countries can be enriched and enhanced through a global strategy to promote genomics for development. Devising this global strategy is a key challenge before us now. In this chapter, we discuss the global nature of genomics and propose the establishment of a Global Genomics Initiative as an example of a global network that can meet this challenge.

Worldwide Scientific Capacity for Development

In his editorial in Science in February 2004,[143] and following his receipt of the InterAcademy Council report on "Inventing a Better Future: A Strategy for Building Worldwide Capacities in Science and Technology", UN Secretary General Kofi Annan noted that "if every nation gains full access to [the] broader world community of science and has the opportunity to develop an independent science capability, its public can engage in a candid dialogue about the benefits and risks of new technologies, such as genetically engineered organisms or nanotechnology, so that informed decisions can be made about their introduction into our lives". One way to accomplish this is through a system of global governance[144] to help achieve a balance between the risks and benefits of new technologies, and ensure that developing countries can take advantage of the benefits of new technologies for development. Using the example of genomics, we argue for action to create a new global governance mechanism that can help achieve this balance – controlling the potential misuse of genomics, while at the same time not losing sight of the all-important promotion of genomics for global health equity.

Balance between Benefits and Risks of Genomics

Traditional models of biotechnology governance tend to be overly risk-focused and advocate restrictions on use, and are not helpful for promoting the benefits of the science for development. An alternative perspective through the lens of global health and development reveals the tremendous potential of this new science to improve global health equity. Consider, for instance, that life expectancy in several sub-Saharan African countries is expected to be less than 30 years in 2010; in the US it is approaching 80 years. Genomics and related biotechnologies have the potential to reduce such stark health disparities, as the WHO points out in its 2002 report on Genomics and World Health. The University of Toronto's study identified the 10 biotechnologies most likely to improve the health of people in the developing world in the next 5-10 years. In chapter 2 these biotechnologies were mapped onto the UN Millennium Development Goals to illustrate their potential contribution toward development solutions. The challenge now is to realize the potential of these technologies, and similar ones identified by developing countries themselves. We propose creating a new global network for governance to achieve a balance between risk management and promotion of genomics for global health.

Inadequate Governance Contributes to Failure of Diffusion of Scientific Innovation

It is likely that, in the absence of a concerted effort, genomics-based tools will not get diffused and widely implemented in developing countries. One reason for this is lack of financial resources, but there are others: a non-receptive policy environment, lack of human resources, few incentives for entrepreneurial activities, insufficient investment in R&D and poor public education and acceptance. All of these can reduce the ability of developing countries to absorb and apply new technologies. Add to this the failure of the devel-

oped world to see the value of ensuring the distribution of benefits of new technologies that can address developing countries' needs and you have a recipe for inequity. Arguably the fundamental reason why new technologies are not implemented is inattention to governance and failure to understand the interplay between these complex issues.

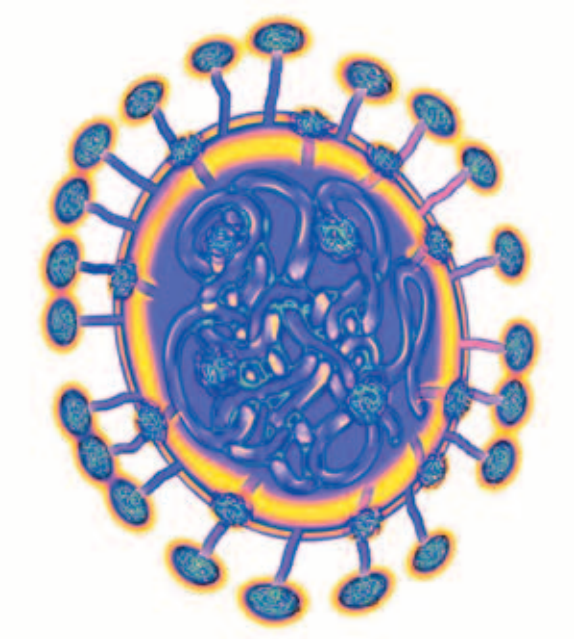
Global Governance to Promote Global Public Goods

Governance for genomics is a challenge not just because of the complexity of ethical, social and legal issues involved, but also because of the rapid evolution of the science. Globalization increases this complexity. So do the significant global public goods characteristics of genomics knowledge.[145, 146] Goods can be defined along a spectrum from pure 'private' to pure 'public' goods. The benefits of public goods such as the ozone layer are enjoyed by all. They are non-excludable and non-rivalrous in consumption. *Global* public goods exhibit a significant degree of "publicness" across national boundaries.[147] The ozone layer is an example - available to all across national boundaries, and not depleted through individual "use". Externalities caused by other activities can have an impact on both quality and quantity of public goods (e.g. chlorofluorocarbons, or CFCs, that deplete ozone). Public goods require some form of governance to maintain them, typically one that transcends nation-states.

BOX 3.1 PUBLIC AND PRIVATE ASPECTS OF THE SARS GENOME

The recent worldwide SARS (severe acute respiratory syndrome) outbreak aptly illustrates both the GPG nature of genomics and its private aspects. In April 2003, Canadian scientists at the Michael Smith Genome Sciences Centre of the British Columbia Cancer Agency sequenced the genome of the SARS virus (which belongs to the family of coronaviruses) for the first time. The sequence of the 30,000 base-pairs genome was shared immediately with scientists all over the world via the Internet. These scientists were able to download and analyze the data directly, and apply it towards their epidemiological investigations in situ, highlighting the importance of sharing the information globally towards local solutions. (This unprecedented achievement points to another critical factor: the convergence of genomics and information technology in the interest of global public health). Going a step further into the realm of private goods, the California-based biotechnology company Affymetrix Inc. was able to use the public genome to create a marketable product – a SARS gene chip for diagnostics. This example points to the continuum of characteristics that genomics possesses, with public input at one end of the spectrum and private goods emerging at the other. In this stepwise process, the public genome provides the basis for the private sector to create a specialized, value-added product.

SOURCE: www.bcgsc.ca/bioinfo/SARS/



The SARS virus belongs to the family of coronaviruses, which are named for their striking corona (crown) of spikes

Genomics is fundamentally about knowledge, which, according to Stiglitz,[148] is the archetypal public good. Genomics knowledge (sequences and databases) is in the public domain. In fact, in a symbolic sense the human genome has been declared a common global heritage of humanity.[149] But the translation of genomics into a marketable product (such as, for instance, a diagnostic tool for malaria) has characteristics of a private good (see Box 3.1). We need a governance mechanism that fosters a balance between the global public goods characteristics of genomics knowledge and the private goods nature of its application. The market is already a major driving force for human health, and most goods and services, and therefore most research and development in health, are geared to the needs of the developed world. If this continues, there is a real danger that the majority of the world's 6 billion people - who do not present profitable market opportunities - will not see the benefits of genomics. We need new mechanisms to address such market failures, perhaps some form of stewardship to maintain the GPG characteristics of genomics.

The GPG characteristics of genomics knowledge inevitably raise issues about access to this emerging resource. This gives us new opportunities to solve global health problems, but it also tests our skills in the evolution and management of international relations, foreign policy, financing, regulation and intellectual property rights. A governance mechanism that can successfully harness these GPG characteristics could be highly effective in promoting genomics for global health.

Other global public goods that have had challenging governance issues and might have relevance to the governance of genomics are biodiversity and the ozone layer (Table 3.1). Depletion of the ozone layer was the major impetus for the Montreal Protocol. The Convention for Biodiversity (CBD) prioritized taking action to deal with biodiversity loss and the potential global public benefits of maintaining biodiversity at various levels. Genomics has similar needs - the option value (enormous potential benefits to global health), as well as the potential misuse of genomics knowledge. A quick look at these GPGs (in Table 3.1) shows certain sim-

TABLE 3.1 GPGS AND THEIR GOVERNANCE

GPG	DRIVING FORCE FOR GOVERNANCE	PRIORITY	GOVERNANCE STRUCTURES
Ozone Layer	Thinning of the layer – effect on human health	Reduction of Chorofluorocarbons (CFCs)	Global convention (Montreal Protocol)
Biodiversity	Loss of diversity Potential use	Species and ecosystem conservation	PPPs Global convention (CBD) National targets
Genomics	Potential use Risk of misuse (ethical considerations)	Improving Global Health	PPPs Global Genomics Initiative?

ilarities and trends. A global governance mechanism for genomics could borrow elements from both the relatively successful Montreal agreement (where most countries acknowledged the dangers of thinning of the ozone layer, and agreed on measures to reverse the trend) and the relatively complex CBD (where there were differences in national-level priorities and incentives were not so clear).

Need for Global Governance for Genomics

Despite the efforts made by individual states in recent decades, in today's increasingly globalized world, it is clear that the governance structure with which we are most familiar - the nation state - is ill- equipped to effectively tackle global issues. New state and non-state actors, new vulnerabilities, new conflicts and new technologies have emerged in recent years, increasing our interdependence and limiting the ability of national policies to address global issues. This is not to say that individual countries cannot and are not taking action to promote genomics. Many developing countries are introducing policy changes to support R&D and enterprise - for instance, new policies in China have increased domestic R&D opportunities and are reducing 'brain-drain'. At the same time, some developed countries and institutions have recognized the place of science in foreign policy, and are designing ways to increase science and technology cooperation with developing countries to help spread the benefits of new technologies worldwide. But a handful of scattered efforts won't achieve the objective – worldwide promotion of genomics for development. A fast-growing science like genomics, with its potential for good and for harm, not to mention the complex ethical, legal and social issues that come with it, needs concerted action at the global level.

Existing Governance Mechanisms may be Insufficient

Are there existing governance mechanisms that could handle the complexity of genomics and achieve the goal of promoting genomics for development?

Treaties and conventions, like the CBD or the WHO Tobacco Framework Convention can work well as governance mechanisms for some matters, but are slow to negotiate and suffer from poor adherence. They are poorly suited to the urgent issue of benefit-sharing in science and technology, particularly for rapidly-evolving sciences such as genomics.

Although recently there have been useful initiatives like the G8 Digital Opportunity Task Force, in general these narrow groupings of countries (G-8, G-20, etc.) are also inappropriate governance mechanisms, especially if the purpose is to reduce global inequities. They are exclusive by nature and often suffer from knowledge gaps, being restricted to certain countries and generally not open to participation from civil society or industry.

World commissions can promote good decision-making by providing a forum for broad input and the integration of diverse points of view and expertise. They can catalyze meaningful political change supported by a public consensus, e.g. the Brundtland World Commission on Environment and Development. But most global commissions are not designed to provide continuity, nor are they agile enough to respond to rapid change.

These existing governance mechanisms seem to be unwieldy, sometimes inflexible, and largely inadequate to address the complexities of implementing genomics in developing countries.

Global Networks can be Inclusive, Flexible and Nimble

The objective is to share information globally and across sectors facilitating informed decision-making that will help close the imminent genomic divide. A global network can do this. Such a loose collaboration among multiple sectors (government, industry, academia, and special interest groups) can provide a common forum for these players to discuss their goals and needs, and creates an environment where consensus can be built to address policy needs.[150]

Global networks have the advantage of speed - they can be launched quickly, and are responsive to rapidly-evolving issues.[151] They are inclusive and non-restrictive in membership (unlike more conventional mechanisms that can take on a "club-like" character). Because of their diverse membership, they can put constructive pressure on governing institutions. They encourage participation from developing countries, and also allow for initiation and leadership from the South. Developing countries with strong biotechnology sectors can take the lead in driving the agenda for health equity. In short, networks encourage speed, equitable participation and flexibility while minimizing bureaucracy and hierarchy.

The Global Genomics Initiative as a Proposed Global Network to Promote Genomics for Health and Development

We at the University of Toronto Joint Centre for Bioethics propose the Global Genomics Initiative (GGI) as a global network to promote genomics for health. The GGI will foster international dialogue for access to and sharing of genomics knowledge; prioritizing health needs in participating countries; and providing the network to help members optimize funding and facilities. It can help countries undertake and achieve specific tasks to implement genomics for health in developing countries. It could coordinate the assortment of existing alliances, partnerships, agreements into a global governance network, and help bridge the gap between bilateral partnerships, PPPs, and alliances at one level and the higher-level governance structures and international organizations like the United Nations and the World Health Organization.

What sets the GGI apart from a risk-focused vision of biotechnology governance is our recognition of, and focus on, the GPG nature of genomics knowledge and its enormous potential for improving health. The use and application of this knowledge towards health and development should be an incentive to people worldwide. A major role of the GGI must be to safeguard genomics knowledge, make it openly accessible and promote its application for developing countries, while minimizing risk of misuse.

What will the GGI do?

The GGI is foreseen to be a global network of concerned citizens, industry leaders, academics, representatives from NGOs, and government officials, with particular emphasis on developing world representation. We are now in the process of bringing together some of the best creative minds from these fields to begin the dialogue and to learn from their experiences so that any decision-making will come from the bottom up - shaped through consultations. Existing public-private partnerships, alliances, networks and coalitions in the arena of genomics and health (such as NEPAD, BIOPAD, the Malaysia-MIT biotechnology partnership) could feed into this network. There is considerable advantage for these partnerships in forging links within a global network - access to knowledge, expansion of partnerships and creation of new scientific capacity through shared resources are obvious benefits.

This group will move forward quickly to set the agenda and define concrete goals for the GGI, both long-term and short-term (Box 3.2):

BOX 3.2 GOALS AND OBJECTIVES OF THE GGI

Overall Mission of GGI: To promote and facilitate broad-based, informed and ethical decision-making about the use of genomic technologies to contribute to global health equity. Among specific objectives of the GGI:

- Promote genomics as a GPG - In this crucial move, the GGI must try to ensure rapid and reliable global access to the world's expanding resources in genomics knowledge
- Encourage equitable participation - The GGI represents a

dedicated effort to hear all voices in the debate on genomics. Participation grounded in the right to involvement is essential for consensus-building and to avoid knee-jerk reactions to technology

- Strengthen capacity in biotechnology - participation in the GGI should promote international and intersectoral exchange of know-how and encourage partnerships between countries (especially developing ones) to build their genomics R&D capacity; and to undertake rigorous evaluation / assessment of policies in R&D investment and human resources
- Prioritize needs and foresight activities - The GGI will undertake surveys or needs assessments, as well as anticipatory evaluations of emerging genomics technologies and respond collectively to new technology or policy initiatives as they arise
- Design financing alternatives - GGI partners can explore and evaluate alternative financing options to fund public and private biotechnology applications for developing countries
- Examine intellectual property rights and other ethical and legal considerations - the GGI could explore different models of intellectual property protection to optimize social utility while maintaining necessary incentives for discovery
- Inspire appropriate regulation - The GGI could also help draft and promote norms and principles for the global harmonization of ethical standards applied to genomic technology research, with benefit-sharing and risk minimization

Challenges for the GGI

Although institutional development will take several years and significant resources, a process like the GGI is likely to yield both short and mid-term benefits in support of global health. In the interest of the credibility, legitimacy, and ultimate success of this exercise, it would be worth taking time now to consult extensively. In Box 3.3 are some of the critical areas that need to be explored.

BOX 3.3 CHALLENGES FOR THE GGI

- Can the GGI establish legitimacy on a global level? The key to this is strong leadership and inclusive membership. Are there champions for such a dialogue within government, industry and civil society, willing to provide both leadership and funding? Can the GGI initiate truly global and inclusive dialogue on genomics?
- Can it minimize complexity and promote equal participation and partnership within the global network, while ensuring that individual countries are provided the opportunity to prioritize their own health goals? This points to the difficulties of coordinating a flexible network
- Can dialogue proceed with enough urgency to provide real value to policymakers given the pace of technological developments in genomics? How can it reverse the current widening of the genomics divide? This is where involvement by developing countries and prioritizing needs will be crucial.
- Can the GGI learn about transparency, inclusiveness and accountability from other multi-stakeholder initiatives?

Envisioning the Future

The initial relative lack of participation by most of the developing world in the Information and Communication Technology (ICT) revolution contributed to what came to be known as the digital divide. The genomics divide between North and South is growing, and the nanotechnology divide is on the horizon. Technologies advance at a faster pace than ever before, threatening to widen the gaps between the developed and developing worlds. International participation in global governance networks like the GGI can help prevent a bleak future of even greater disparities between industrialized and developing countries. Appropriate action now by the world community - governments, citizens and experts from industry and academia - can shape a more equitable global future.

We have described the Global Genomics Initiative as a genomics-specific model for the general application of science and technology to help achieve the MDGs. As outlined in box 3.2, the GGI has several objectives, among them improving global genomics policy, encouraging the idea of investment in human capacity and R&D, promoting entrepreneurial activities in the area of biotechnology and genomics and playing an active role in forecasting activities. Science and technology can contribute to economic development in developing countries. Developing countries can establish and strengthen scientific institutions through improving the science policy environment. One way to improve science policy is through exchange of information with other countries, especially those with success stories to share. A global science and technology network, based on the model provided by the Global Genomics Initiative, may help countries use multi-sectoral dialogue to develop forward-thinking global science policy for development.

The Role of the United Nations in the Global Genomics Initiative

The Global Genomics Initiative aligns well with Kofi Annan's announcement of the UN's intention to convene a global policy network on biotechnology.[152] This announcement confirms the prominence of biotechnology as a global force of change. It underscores both the urgency for a global network for biotechnology as well as shows evidence of the UN's initiative and leadership in biotechnology. Others have noted that by facilitating the emergence of global policy networks, the UN can help strengthen the capacity of state and non-state actors to develop global public policy, while increasing its own effectiveness and credibility.[153] We now extend these arguments to apply to the Global Genomics Initiative, and call attention to the UN's potential role in helping the GGI achieve its goals – and thereby helping to achieve the Millennium Development Goals. Just as the World Health Organization can promote the production of health as a global public good,[154] we envision the UN system as promoting genomics as a global public good. The GGI can assist by playing the role of facilitator among multi-sectoral partners, including international agencies through providing a platform for reliable and freely accessible information for genomics knowledge.

Summary

An interdependent world in which the greatest majority has limited access to good health while the quality of life of the minority continues to improve is a recipe for social confrontation. The UN Millennium Development Goals aim to decrease these development gaps, and achieving them is well within human capacities. The Global Genomics Initiative could be instrumental in developing common understandings among governments and their citizens, corporations, and non-governmental organizations, setting a strategic direction and mobilizing commitment to a healthier, more equitable world. The GGI can help to realize the benefits of genomics and biotechnology for the UN Millennium Development Goals.

— CHAPTER FOUR —

BUILDING GENOMICS CAPACITY IN DEVELOPING COUNTRIES

Genomics holds clear benefits for developing countries, and chapter 2 of this report indicated the ways in which genomics and related biotechnologies can serve the Millennium Development Goals. The challenge is how to implement these technologies in developing countries within the next five or ten years. The ability of a country to solve development problems and sustain economic growth depends to some extent on its institutional structures and capabilities in science and technology. In this final chapter of this report, we assert that developing countries with the scientific capacity and institutional arrangements that allow creation, utilization, adaptation or diffusion of this new field of science and technology are well-positioned to harness genomics for development. We support our argument with examples of strategies that some countries have followed to institute learning processes that can help them build their national systems of innovation in biotechnology, and conclude with lessons learned and recommendations.

Transfer of Technology *and* Science – Building Science Capacity in Developing Countries

After the Second World War, technologies were transferred from the United States to reconstruct war-torn Western Europe.[155a,b,c] Europe's success led naturally to the mistaken belief that the application of the same model to encourage economic development in developing countries.[156, 157] It was believed that technology transfer would kick-start the engine of growth, the benefits would trickle down throughout the economy and result in further development of technological capacity. It was considered unnecessary, even extravagant, for poorer income countries to do fundamental research since they were primarily seen as technology users and dependent on imports from technology producers.[158]

Today the growing view is that mere technology transfer does not always guarantee solutions to problems in developing countries, especially if they are not of relevance to industrially advanced countries. For example, disease profiles and health needs vary the world over, and the pharmaceutical companies in the industrialized world typically target health problems in higher-income countries. The market-driven strategies of the pharmaceutical industry are not sufficient to steer technological innovation to solve development problems. Research on treatments for diseases of the poor, which generally have higher incidence and prevalence rates in lower-income countries, remains neglected.[17] The imbalance in global R&D efforts strengthens the case for developing countries to invest in indigenous scientific capacity to help meet their own health and development needs.

Contrary to expectations, technology transfer initiatives in developing countries have met with limited success. Indeed, research has shown that the benefits of technology transfer are best harnessed by those countries that have built the capacity to absorb, use and even adapt technology.[159, 160] Countries need to build capacity in high quality basic research in order to benefit economically from science and technology.[161] This includes trained human capital, as well as investment in institutions, equipment, and networks.[162] Countries like Brazil, China and Cuba have invested in science and technology for decades and have consequently created a strong science base. These scientifically proficient countries have to some extent been able to absorb and keep up with the advances that the genomics revolution brings by building upon their strong scientific foundations. Some of these countries are even beginning to enjoy private sector successes in this new field.

It follows, therefore, that genomics and biotechnology will probably make the most sustainable and effective contributions to development in those developing countries that possess capacity in these fields. Developing countries can best benefit from these technologies if they are active participants not just in the use of technology but indeed in all stages of innovation including research, development, and production. For example, several international public-

private partnerships (PPPs) have recognized the fact that biotechnologies developed to address health problems in developing countries will be most sustainable if accompanied, at the very least, by training of human resources – one aspect of innovation (Box 4.1).

BOX 4.1 GAVI AND THE ROTAVIRUS VACCINE

Some international coalitions and public-private partnerships plan to develop technologies specifically for use in developing countries, with the help of these countries as partners. An example is the rotavirus vaccine project initiated by the Global Alliance for Vaccines and Immunization (GAVI). GAVI has selected the Program for Appropriate Technology in Health (PATH) to lead a three-year US$30 million project to develop a safe and effective rotavirus vaccine for developing countries. Rotavirus is the leading cause of severe diarrhea and diarrhea-related deaths in the world. Although access to clean water is vital to eliminate rotavirus infections, a vaccine to induce immunity against infection is also essential to control the disease, and could save up to 1.5 million lives. According to Tore Godal, Executive Secretary of GAVI, "rotavirus vaccine development represents an important contribution to reaching the Millennium Development Goals."

Two aspects to this project are noteworthy. Firstly, GAVI's goal is to make the rotavirus vaccine available to children in developing and industrialized countries at the same time. This simultaneous transfer of technology to both industrialized and developing countries is unprecedented. In the past, vaccine manufacturers would conduct trials and introduce new vaccines in countries with the largest profit potential. The product would become available in developing countries, where the greatest burden of disease occurs, only after 15-20 years. By working with vaccine manufacturers and developing country governments, the PATH rotavirus project aims to make the vaccine available in 5 years. The second novel aspect is that GAVI is planning to ensure that developing countries are prepared to receive and utilize this new vaccine. They will set up surveillance networks to monitor the disease before and after the vaccine is introduced, and educate the medical community, policy makers and users about the public health benefits of the vaccine.

SOURCE: www.vaccinealliance.org

The building of scientific capacity cannot take place overnight. It is a long, complicated and challenging process for both low and high-income countries and promoting science intensive fields like genomics in the resource-poor environments of developing countries is especially challenging. Moreover, capacity building goes far beyond just building expertise in science. Equally important is expertise in, for example, financial, regulatory and legal matters. Private sector involvement is another critical factor. In countries like South Korea and China, and more recently in India, market liberalization has played an important role in recent years, helping these countries develop their private sector and encourage companies to attract foreign investment and develop resources.[163] Governments may have to play a supportive role for these companies through the establishment of "Science Parks", tax breaks or rebates for investing in research and development and the establishment of institutional and regulatory support structures. Clearly, there are many factors that contribute to scientific capacity: national infrastructure (e.g., communication and transportation systems, legal and regulatory structures); government policy on science and technology issues; the pool of scientists, engineers, and other trained workforce; academic institutions and other research facilities; and private firms that can produce and market technology products.

Learning is Key to Building Capacity in Science and Technology: National Innovation Systems in Developing Countries

One way to think about building scientific capacity is as a process of learning and innovation – a sustainable approach to enable developing countries to capture the benefits of genomics for the MDGs. Creating synergistic inter-linkages between the learning processes that occur within all economic activities including R&D, marketing, production, and development is essential to spur innovation. This network of interactions is the foundation of a national system of innovation.

The national system of innovation (NSI) represents the institutions that contribute to the creation, diffusion, and use of new economically useful knowledge in a specific country and the linkages and synergies between the institutions.[164a,b,c] These institutions include not only formal ones like firms, universities, research centers and government, but also institutions in a wider sense, such as social norms and laws (for example intellectual property rights).[165] Knowledge creation, diffusion and use are at the core of innovation systems frameworks. This involves non-linear, multidirectional flows between the various actors. There are various ways in which the elements of the NSI can interact for knowledge creation, diffusion and use. For example, they can involve technical, commercial, legal, developmental, social, financial, or regulatory interactions.[166]

Although the NSI concept has been studied for over a decade, its application to developing countries is relatively recent. Some researchers have concerns about the applicability of the NSI framework in developing countries.[167] One aspect that Arocena and Sutz emphasize is that innovation in developing countries is often within micro-realms instead of being systemic. They warn against importing "turn-key" institutions and policies from industrially advanced countries to developing countries based on tacit assumptions, which may not be true in these countries. In their study on innovation systems in Thailand, Intrakamnerd et al. stress the need to examine factors that hinder technological learning.[168] The perception is that innovation systems in developing countries are weak and fragmented. Lundvall and colleagues[169] also agree with this notion that NSI studies in developing countries should be adjusted to accomodate different learning environments. They argue that in the context of developing countries it is important to shift the emphasis of NSI studies to system construction and promotion. They also point out that there is a need to apply a broader concept of innovation when it is used in the context of developing countries. For instance, developing countries may more often (relative to higher income countries) be able to leverage the richness of their local and traditional knowledge. Therefore, the innovative learning that takes place in many developing countries is not always in the realm of science-intensive endeavors or in high-tech activities. Other analysts have observed that, when applied to developing countries, innovation can be perceived as the process that companies use in their learning of design and production that is new to them.[170] Imitations and incremental improvements in product design and production processes may form a significant part of local innovation in developing countries.

Developing countries that are now overcoming barriers and are fostering learning processes in their institutions and building scientific capacity are of particular relevance to the question of how a country can build its NSI. The Canadian Program on Genomics and Global Health is in the process of conducting a study of the health biotechnology innovation systems of Brazil, China, Cuba, Egypt, India, South Africa and South Korea, all of which have relatively active biotechnology industries.[171] It has focused on identifying the main actors in the health biotechnology innovation systems under study, i.e. by examining the roles of government, private firms, R&D system, the education system etc in the health biotechnology innovation process. The study has also explored the extent and patterns of linkages between all the actors in the NSI systems. Where

linkages extended beyond national boundaries, information was collected on the role of international linkages in the development of genomics/health biotechnologies in these countries. The impact of domestic markets and export markets on innovation systems was also studied. The social environment and public acceptance of genomics/health biotechnologies in the countries under study will be included in the analysis.

The NSI framework is increasingly guiding policy in various ways in developing countries. In South Africa, for example, the Biotechnology Advisory Committee (BAC) prepared a biotechnology strategy following an NSI approach with the aim to increase biotechnology capacity in the country. The identification of key institutions such as governmental agencies to promote scientific capacity, human capital and the necessary linkages between various actors and institutions resulted in a recommendation by BAC to create Regional Innovation Centres (RICs) as nuclei for the development of biotechnology platforms that can effectively launch new products and services (see Box 4.2).

BOX 4.2 SOUTH AFRICA'S REGIONAL INNOVATION CENTRES

In order to stimulate the growth of biotechnology in South Africa, the Biotechnology Advisory Committee (BAC) presented its recommendations to the government in 2001. National priorities for biotechnology involve human health, food, security and environmental sustainability. Factors that contribute to strengthening biotechnology include a government agency that supports biotechnology through building scientific capability and human capital. Successful commercialization of public sector-supported R&D requires strong linkages within the National System of Innovation. A key recommendation in light of this by the BAC is the creation of several Regional Innovation Centres (RICs) to act as nuclei for the development of biotechnology platforms that can effectively launch new products and services. The main goal of these RICs will be economic growth in the biotechnology sector through innovation. The RICs will be designed to support close collaboration between academic and business ventures. New products create new intellectual property, and this needs to be accompanied by the simultaneous creation of support structures for the protection and appropriate exploitation of the IP generated. BAC stresses that no such venture will be successful, however, without full engagement by the government – and the government must take responsibility for promoting public understanding of biotechnology, and for ensuring that new biotechnology products and services do not threaten human well-being.

The response to these recommendations has been swift. South Africa's bid to commercialize biotechnology is forging ahead with the establishment of three new RICs, launched in March 2003. The science and technology department has allocated R400 million (US $50 million) in funding to centres in Gauteng, KwaZulu-Natal and Western Cape, each drawing on regional strengths. The Cape Regional Biotechnology Innovation Centre has been given a mandate to support projects in the areas of human health and industrial bioprocessing. Already drawn up is a short list of 19 projects. These projects include initiatives to develop drugs from indigenous plants to treat diseases such as malaria and tuberculosis, as well as vaccines to combat various childhood diseases, rabies, and the human papilloma virus, which can lead to cervical cancer.

Although these are encouraging developments, there is considerable scepticism about the future success of these RICs and it will take some time and careful evaluation to determine their contribution to the country's innovation system.

SOURCE: http://www.safrica.info/what_happening/news/biotech.htm

Options for Developing Countries to Build Learning Systems

The health biotechnology innovation country case studies discussed in the previous section should yield useful information that could help identify factors and policies that foster biotechnology innovation in the developing world. They may also provide insights into potential barriers to development. Other developing countries could apply the experiences of these countries, within limits, to help develop their own innovations systems and reap the benefits of biotechnology. While there is no "one-size-fits-all" model, there are lessons to be learned from these countries that have already had some successes in creating strong and vibrant biotechnology sectors.[172] And even where the NSI framework is not clearly spelled out, developing countries can work on particular elements of the framework in their effort to build capacity in biotechnology. For instance, they could focus on building human resources by training scientists in genomics and bioinformatics. Alternatively, they could explore ways of adapting existing biotechnologies to low-resource settings. The following examples illustrate how developing countries can take advantage of existing programs with organizations that carry out these functions.

Building a Science Base by Re-energizing Academic Institutions

Strengthening academic institutions and improving their capabilities in the new life sciences is an essential component of the National System of Innovation, as is the creation of a pool of trained scientists. Governments of developing countries will have to invest in higher education, with a focus on the sciences, in order to create the human capital and knowledge base to enable research and development. Given the paucity of financial resources, most developing countries agree that this investment has to be careful and measured. One way forward for these countries in the short term may be to invest in specialized departments or research centers, perhaps within existing universities, that focus on particular research areas and have clearly defined research goals – such as the development of technology for bioremediation. In Thailand, the National Centre for Genetic Engineering and Biotechnology (BIOTEC) was instrumental in setting up the new Microbial Genetic Engineering Unit at Mahidol University, which focuses on the study of microorganisms and also shares and disseminates genetic engineering techniques through training and education. One of the projects the Unit is currently conducting is the development of a strain of *A. quadruplicatum* bacteria genetically engineered to be capable of controlling and eliminating disease-carrying mosquito larvae in contaminated water. BIOTEC allocates approximately 70% of its R&D budget to universities and research institutes, one aspect of which is creating biotechnology-focused departments at universities in Thailand; the remaining 30% is used for in-house research projects. Its overall mandate is to provide the resources for the country to develop the critical mass of researchers necessary to achieve Thailand's national R&D targets in biotechnology.

Another way forward is to take advantage of training opportunities in partnership with academic institutions in the industrialized world. Such programs are offered by many organizations. One such organization is the Fogarty International Center (FIC) of the National Institutes of Health (NIH). In October 2002, FIC and seven partners announced six new research and training grants to support international collaborations in human genetic sciences for an International Collaborative Genetics Research Training Program. FIC's partners included the World Health Organization, the National Human Genome Research Institute (NHGRI), the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), the National Institute on Drug Abuse (NIDA), and the National Institute of Environmental

Health Sciences (NIEHS). The combined financial commitment from FIC and its NIH partners is approximately $2.3 million for the first year of these five-year awards. Total support will be approximately $11.5 million over the next five years.

The aim of the program is to apply the science of genetics to help reduce health disparities between developed and developing countries. For example, Columbia University, in collaboration with scientists at the University of Zulia in Venezuela, will provide training in the genetics of common heritable disorders relevant to Latin America and the Caribbean, with a focus on neurodegenerative diseases. Through these types of specific partnerships, this program aims to enable advances in human genetics research by enhancing technical capacity in genetic science in developing countries.

In addition to providing training in genetic sciences, these projects propose to address the ethical, social, and legal implications of performing genetics research in developing countries. Therefore, the collaboration between Columbia University and the University of Zulia will not only include training in human genetics, independent research projects, and learning the process of developing low-cost diagnostic methods for neurodegenerative diseases but also addressing the associated ethical issues of human genetics. The program was developed in consultation with scientists and health professionals from developing countries. The program organizers felt that this was vital in identifying those public health needs in the developing world that can be addressed through genetics and genetic technology with sensitivity towards the ethical, social, legal, and cultural issues in developing countries. Below in Box 4.3 are examples of three FIC projects incorporating both the technical training to improve capacity in developing countries and the ethical, social, and legal implications related to the research.

BOX 4.3 EXAMPLES OF THE PROJECTS THAT HAVE RECEIVED FIC AWARDS

Researchers at Yale University School of Medicine, in collaboration with the Faculty of Medicine at Chulalongkorn University in Bangkok, Thailand, will conduct a research-training program in the genetics of drug dependence and the ethical, legal, and social implications of genetics research. Thai researchers will receive short- and long-term fellowships to train in the United States. The project will also support field exchange training rotations in Thailand for U.S. trainees.

Johns Hopkins University will collaborate with researchers at Peking Union Medical College and Peking University in Beijing, China, to provide training in the principles of genetic research on complex disorders, including birth defects and chronic diseases. Building expertise in the ethical, social, and legal implications of human genetics research will be an integral part of the curriculum.

University of Pittsburgh, in collaboration with the Indian Statistical Institute Centre for Population Genomics in Calcutta, India, will build genetic-epidemiological research capacity in India. Their research-training project focuses on genetic epidemiology and ethical conduct of human genetics research in India, with particular emphasis on statistical and computational genomics and molecular genomics. It will train personnel who will develop large-scale genetic epidemiological studies in India; and it will foster collaborations in human genetics research between scientists in India and the United States.

SOURCE: http://www.nih.gov/news/pr/oct2002/fic-22.htm

A potential point of entry for developing countries is the field of bioinformatics – a relatively small investment compared with expensive laboratory infrastructure.

Bioinformatics can allow developing countries to participate in quality research with relatively few resources. The UN Science and Technology Task Force has identified bioinformatics as one field of biotechnology that would encourage local research. There are several training opportunities in this field for developing country scientists (Box 4.4).

BOX 4.4 RESEARCH AND TRAINING IN BIOINFORMATICS – A SPECIAL FOCUS

With appropriate training and software, computers and internet connections, developing countries can develop human resources to study pathogen sequences and biochemical pathways using genomics and bioinformatics. Most bioinformatics algorithms and a lot of genomics data are "open source" or freely available on the Internet. The Special Program for Research and Training in Tropical Diseases (TDR) provides training opportunities for scientists. It is an independent global program of scientific collaboration, established in 1975 and co-sponsored by the United Nations Development Program (UNDP), the World Bank, and the World Health Organization (WHO). In 1994, TDR helped establish five international parasite genome networks to provide the opportunity for scientists from disease endemic countries to participate and collaborate in genome and post-genome projects. Following this, the TDR initiative on developing capacity in bioinformatics was launched in 2001. It has helped to establish regional training centers for "Bioinformatics and Applied Genomics" located in Brazil, South Africa, India and Thailand.[173] The rationale was that capacity in bioinformatics is required for both basic research as well as the development of new biotechnology applications in disease control. TDR aims to:

- Train 20-30 disease-endemic country (DEC) scientists ('trainers') in bioinformatics in order for them to conduct local bioinformatics training in Africa, Asia and Latin America in the next five years
- Establish sustainable regional networks of centres and expertise for the promotion and integration of bioinformatics and DNA technology in basic research and management of tropical diseases using existing and newly developed infrastructure
- Establish a distance-learning program for bioinformatics in DECs

As a first step – "training the trainers" – the International Training Course on Bioinformatics and Computational Biology Applied to Genome Studies was held in 2001, in Brazil. The objective was to develop a multi-disciplinary and international network for bioinformatics applied to pathogen genome research and to prepare participants to teach similar courses in their home countries. The next steps are to initiate regional training courses in Africa, Asia and Latin America, and a Bioinformatics Career Development Grant for exceptional scientists identified from these courses. In the longer term, Masters and Doctoral training programs will be developed. The centres in South Africa, Brazil, India and Thailand will provide regional training courses in bioinformatics. Despite the fact that TDR's bioinformatics initiative is quite young, considerable progress has already been made in strengthening institutions and training researchers from developing countries, helping them to reach self-reliance in this field of modern biological research.[174]

A similar effort has been initiated at the South African National Bioinformatics Institute (SANBI) at the University of the Western Cape, South Africa: the Bioinformatics Capacity Development Research Unit. This initiative recognizes the competitive opportunities in bioinformatics for smaller, less developed countries since bioinformatics does not require prohibitively costly infrastructural investment. SANBI emphasizes biological research located in and focused on Africa and African concerns. Its goals include the development of an online, specialized resource for genomics and genome informatics; capacity development in genomics and bioinformatics in South Africa; and the development and implementation of genome annotation methods. The

Unit aims to heighten awareness of bioinformatics in South Africa and to assist the country in making optimal use of this technology. It offers services in databases - nucleotide, protein, structure (including the human genome sequence and derived data); software tools for bioinformatics / genomics; countrywide training in bioinformatics and genomics; and a bioinformatics support network of South African scientists. The first workshop for African scientists on bioinformatics, held in 2003, attracted scientists from several African countries. A bioinformatics network of researchers in seven African countries has been established with the Unit as the hub.

International Collaboration to Adapt Technology to Low-Resources Settings

One barrier to development is that technologies developed in the industrialized world do not rapidly find applications in developing countries. Countries that have some scientific capacity can work with organizations like the Sustainable Sciences Institute or the International Development Research Centre (IDRC) to adapt existing technologies to their needs. As a nonprofit entity, the Program in Appropriate Technologies for Health (PATH) plays a critical role in providing technology-related services and innovative solutions to health care problems. It works as a partner with development agencies, governments, NGOs and private industry to achieve: rational choice of health care technologies; widespread and effective use of technologies; sustainable systems of supply and support; and global standards of safety and quality.[49]

The Sustainable Sciences Institute (SSI) is another nonprofit organization involved in improving global public health by helping scientists in developing countries gain access to the technologies needed to address local problems related to infectious diseases.[175] Over the past decade, SSI has conducted its successful Applied Molecular Biology/ Appropriate Technology Transfer Program (AMB/ATT) to transfer molecular biological techniques to developing countries for application to public health and the biomedical sciences. The program consists of workshops covering various phases of scientific methods, from the introduction of molecular biology and epidemiology to their implementation in the field. Courses are taught in laboratories in the host country with available local resources and in the local language. They emphasize a rigorous, yet low-cost scientific approach. Participants gain hands-on technical experience with molecular biology techniques, and training in good laboratory practices and scientific methodology. Experiments focus on the application of these techniques to locally prevalent infectious disease problems. Participants are trained to formulate research questions and design scientific projects, and ultimately develop grant proposals for external funding. Box 4.5 shows one example of a molecular diagnostic tool recently developed in partnership with developing country scientists and adapted for use in Nicaragua, Ecuador and Sri Lanka.

BOX 4.5 SUSTAINABLE SCIENCES INSTITUTE AND THE IMMUNOSENSOR

A recent joint project of SSI and the Department of Electrical Engineering and the School of Public Health at University of California, Berkeley has resulted in the "ImmunoSensor". This low-cost, point-of-care diagnostic tool combines cutting-edge electronics with biological assays. The ImmunoSensor is a small (~1 mm^2) computer chip, based on the same technology as the Pentium® computer chip but with diagnostic capabilities. Batch fabrication processes allow this technology to be manufactured at low cost. The chip can perform data analysis and processing, which makes the ImmunoSensor portable (data is recorded by a small hand-held reader), disposable and affordable (under US$ 0.50 per test). The chip can be designed to allow the simultaneous detection of multiple pathogens or antibodies. The prototype ImmunoSensor diagnoses dengue, the most prevalent mosquito-borne viral illness. SSI is currently coordinating field trials of

the ImmunoSensor for the diagnosis of dengue in Nicaragua, Ecuador and Sri Lanka in partnership with local scientists. The first field trials of the dengue ImmunoSensor began in Nicaragua in March 2004. Additional funding has been obtained for development of HIV / AIDS diagnostic tests and viral load assays using the ImmunoSensor platform. SSI and UC Berkeley are planning to develop, validate and begin commercialization of the ImmunoSensor in developing countries over a two-year period. SSI also intends to devise novel business strategies for these countries to develop and market products tailored to their own needs.

SOURCE: www.ssilink.org

Improving the Policy Environment and Encouraging Regional Cooperation

Governments can promote innovative learning through visionary technology or economic policies. Alvaro Díaz, Chile's deputy economy minister, has recently unveiled a policy "Biotechnology as a tool for development and well-being" that aims to boost biotech research and to help companies use biotechnology to strengthen the country's economy.[176] The policy has four main objectives: updating laws that concern biotechnological activities; creating an overarching regulatory body; developing scientific and technological capacity; and promoting entrepreneurial innovation in biotechnology. Although many have welcomed this policy as a step in the right direction, others fear that it does not sufficiently reflect the concerns of small and medium-size biotechnology companies and consequently may not foster innovation on a large scale.

A somewhat more focused policy in Cuba provided political support for biotechnology over the last few decades that allowed for government investment in developing modern laboratories and incubation centers. These research centers worked primarily on health biotechnology. This investment has paid off, with the discovery and patenting of meningitis-B vaccine in the late 1980s. The vaccine has now been licensed to GlaxoSmithKline, which will market it in Europe and the USA. Scientists in Cuba tend to play an active role in national policy-making, and this in turn strengthens scientific research institutions. For example, the directors of the Centro de Ingeniería Genética y Biotecnología (CIGB), and of the Carlos Finlay Institute, are members of the State Council. The fact that they play an influential role in decision-making underscores the importance of informed policy-making in fostering innovation.[177]

Creating the appropriate policy environment for learning and innovation requires multi-disciplinary dialogue. In partnership with other institutions, the University of Toronto's Joint Centre for Bioethics is in the process of conducting a series of Genomics Policy Executive Courses in developing countries, with funding from Genome Canada and the International Development Research Centre (IDRC). The purpose of these courses is to help draw necessary attention to genomics policy in these countries in order to better prepare them to assimilate and apply genomics technologies to their needs. The main objectives are:

- To familiarize participants with the current status and implications of genomics and biotechnology for health in their country, and to provide information relevant to public policy
- To provide frameworks for analyzing and debating the policy issues and related ethical questions, and to help understand, anticipate and possibly influence the legal and regulatory frameworks which will operate, both nationally and internationally
- To begin developing an opinion leaders' network across different sectors (industry, academic, government, and voluntary organizations) by sharing perspectives and building relationships

A wide range of topics is covered, starting with recent scientific advances in genomics, followed by discussions on business models in genomics and biotechnology, intellectu-

al property rights and regulatory frameworks, public engagement and internet-based opinion leaders' networks to foster multi-sectoral dialogue.

Four courses of the series have been held, in Africa, India, the Eastern-Mediterranean Region, and Latin America/Caribbean region.[178] The first was held in Nairobi, Kenya in March 2002 and attended by scientists from 10 African nations. Some of these already have strong biotechnology capacity (like South Africa and Kenya) while others gained from the course by sharing experiences and establishing networks. The course in India was held in January 2003 and was attended by scientists and representatives from academic centers and industry, regulatory officials, representatives from the legal sector, NGOs and journalists.[179] The one for Latin America and the Caribbean was held in Caracas in May 2004, with participation from the various stakeholder groups from most countries in Latin America plus two Caribbean countries. The multi-sectoral participation at each of these courses ensured a rich dialogue on the potential for genomics to address health needs. The dialogue continues via Internet-based opinion-leaders' networks for each region.

A number of recommendations emerged from each course and Box 4.6 shows the recommendations from the Eastern-Mediterranean Region course, held in Muscat, Oman, in September 2003. The WHO's Eastern Mediterranean Regional Office (EMRO) has reviewed these recommendations. Soon after the course, Ministers of Health from the region, at the 50th Regional Committee Meeting held in October 2003, urged Member States to establish national bodies for genomics and biotechnology to formulate strategic vision for creating public awareness and for developing biotechnology for equitable health care in the region.[180] On close examination, it is evident that many of these can be applied to developing countries elsewhere in the world (e.g. the recommendation to conduct foresight studies and health needs assessment) but others may be more specific to the region (for instance, in India there was emphasis on leveraging the country's strengths in traditional knowledge, genomic diversity and biodiversity).

One more course is planned for late 2004, for Southeast Asia.

BOX 4.6 RECOMMENDATIONS ADAPTED FROM THE EASTERN-MEDITERRANEAN REGION COURSE

The workshop participants recommended that EMRO urge national governments to prioritize genomics for health and health biotechnology. Effective advocacy material should be provided to political leadership to emphasize links between health biotechnology and poverty alleviation, public health, and the need for transfer (and internalization) of science and technology.

Each member state should create an effective National Body on Genomics, Biotechnology and Health. The membership should be multisectoral and include youth, women, and civil society. EMRO, the Organization of the Islamic Conference Standing Committee for Science and Technology (COMSTECH), and other groups should facilitate coordination and networking among national biotechnology bodies to exchange information, expertise, training, and regional cooperation in production and utilization of health biotechnology.

EMRO, in collaboration with member states and their National Biotechnology Bodies, should conduct a national survey / inventory / situation analysis / needs assessment of health biotechnology innovation systems, including scientific and management capacity, government policies, legislation and regulations, intellectual property policies, private sector activity, and strengths / weaknesses, opportunities and threats.

Based on evidence from the national survey, governments of member states should develop and adopt, at the highest level, a national biotechnology strategy.

The National Biotechnology Body should encourage academic institutions including schools and universities, to include health biotechnology topics within their curricula and create specialized programs and degrees where appropriate. There should be particular emphasis on information and communication technologies (ICT) and bioinformatics.

The National Biotechnology Body, in collaboration with the relevant ministries, should develop a plan to integrate genetic and genomics products (e.g. diagnostics, vaccines, therapies, and other genomic priorities), within public health programs. Emphasis should be on accessibility and equity to improve health of the poor.

There is a need for strong personal commitment to strengthen the initiative on genomics and biotechnology to improve health and well being of people in the EMRO Region. Workshop participants, as well as other concerned individuals, are encouraged to actively engage in the implementation of these recommendations.

A common sentiment among the participants in all the courses held so far was that a key requirement for building scientific capacity is access to scientific knowledge. It is important to achieve a balance between the requirements of the scientific and technological research community for open access to the most current scientific information and acknowledging and maintaining a healthy intellectual property rights regime that provides incentives to various stakeholders.[181] Understanding, interpreting and effectively leveraging international agreements on intellectual property rights and trade is an essential component of the learning process to build scientific capacity. Furthermore, foreign investment rises when countries can ensure intellectual property protection. In the last decade, a number of developing countries have expressed discontent with international intellectual property rights and their perceived bias towards the industrialized world. But interestingly many observers feel that developing countries are moving towards a paradigm in which they are not only adopting, but also adapting, intellectual property laws to serve their own needs. The recent failure of the Cancun talks, in mid-2003, points in fact to success when viewed from an alternative perspective – the recognition by Brazil, China and India that developing countries can use international trade laws to their advantage to strengthen their negotiating positions. Almost all Ministers from the developing countries have reaffirmed their faith and confidence in the multilateral trading system and appear to support the sentiment reflected in the statement made by Celso Amorim, Foreign Minister of Brazil: "the WTO is irreplaceable not only for Brazil, or for members of G-20, but also for all developing countries."[182]

Many developing countries and international organizations agree that training in patent law and intellectual property protection is urgently needed. In 2002, the Rockefeller Foundation launched the Centre for the Management of Intellectual Property in Health Research and Development (MIHR). The aim of MIHR is to help build technology management capacity in developing countries, and especially to conduct research and share best practices in the management of intellectual property to promote global health. This international organization is based in Oxford, United Kingdom, but has linkages and activities all over the world. MIHR has developed a handbook of best practices, conducted workshops in South Africa, Egypt and India, and is now exploring partnerships with the Indian Council for Medical Research, South Africa's Medical Research Council and other technical agencies in developing countries. One of MIHR's primary goals is to raise the stature and build capacity of technology managers and technology management offices in publicly funded health research institutions in developing countries – so they can enter into sound, viable "indigenous" public-private partnerships that are accountable to the public interest.[183, 184] A major challenge that still remains, and that is relevant to many devel-

oping countries, is how to recognize and protect traditional knowledge within this international IPR regime. Some commentators believe that the intellectual property rights designed to protect commercial innovations are inappropriate for protecting traditional knowledge.[185] In response, developing country policy makers, who deal with trade, development, agriculture, health, culture, and the environment, have begun to give careful consideration to the implications of intellectual property laws on traditional knowledge and indigenous peoples. For example, the Philippines government has passed the Traditional and Alternatives Medicine Act (TAMA) of 1997 or Republic Act 8423, which acknowledges and institutionalizes the ownership of knowledge of traditional medicines by indigenous societies.[186] According to this law, when outside users draw on such knowledge, the indigenous societies require them to acknowledge its source and demand a share of financial return that may come from its authorized commercial use. There are now several anecdotal examples, from all over the world, of countries harnessing and protecting traditional knowledge – like India's overturning of the controversial turmeric patent and the South African San Council's agreement with the Council for Scientific and Industrial Research (CSIR) of South Africa that recognizes the San people's traditional knowledge of the Hoodia plant's medicinal properties.

Encouraging Private Enterprise

One important goal of strengthening the scientific base and improving science policy in developing countries is the generation of new goods and services of significance to improve health in developing countries. Stimulating the biotechnology industry in developing countries is one way to achieve commercialization of R&D. As mentioned earlier, forward-looking economic policies have tended to improve conditions for private enterprise in general in recent years, allowing countries with large market potential like India and China to enjoy considerable growth in the private sector. These countries took steps to liberalize their economies and strengthen protection of intellectual property rights in order to create incentives for foreign direct investment.

International collaboration between companies may also help to foster private sector growth in developing countries. Recently Genematrix, an early-stage Korean biotechnology company, entered into a collaborative agreement with Variagenics, a U.S.-based pharmacogenetics company. Through this partnership, Genematrix hopes to gain expertise in applying pharmacogenomics to all phases of drug and diagnostic development from discovery to commercialization and bring important diagnostic products to the South Korean market. In return, Variagenics will benefit from GeneMatrix's genomic data from targeted Asian populations.

South-South collaboration between companies in developing countries can also create new opportunities for entrepreneurs. Cuba's Heber Biotech, a semi-private company, has helped to commercialize its biotechnology products. By 1998, Heber Biotech was recording about $290 million (U.S.) annually in sales of hepatitis B vaccines and pharmaceuticals in 34 countries.[172] Now the company is entering into partnerships with other developing countries. In 2001, it established a joint marketing venture with Kee Pharmaceuticals of India. The company's new division 'Kee Biogenetics' has launched India's first recombinant DNA streptokinase, "Cardiostrep," owned by Heber Biotech, which is capable of dissolving coronary clots and preventing heart attacks. The company aims to use special pricing to access the $11 million Indian market.[187]

Specific initiatives to help small and medium enterprises in biotechnology are a recent and promising development in some countries. The Egoli BIO life sciences incubator, launched in February 2003, is a business incubator that aims to nurture small, medium and micro-sized biotechnology enterprises for commercialization. Egoli BIO seeks to act as a "development conduit for the commercialization of life sciences research, products, services and technology platforms" in South Africa.[188] The company works closely with

Biopad (Biotechnology Partnership for Development), itself charged with stimulating economic development, contributing to job creation, and building world-class skills and technology platforms to sustain and continue development.

Creating incentives for private enterprise is not likely to be sufficient for private sector growth without simultaneous growth in human capital. China, for instance, has been trying to attract back its scientists trained overseas through various incentives (some of these somewhat controversial – such as limiting the time spent abroad during post-doctoral training). Critical factors to consider for the growth of private firms in developing countries include the relatively small academic base, the lack of human capital and financial resources, the absence of a market-oriented research culture, few large national (or even international – although this is changing gradually) biotechnology companies, and inexperience by academic institutions in mechanisms to transfer research findings to companies.

Finally, the linkage between basic/applied research activities and commercial enterprise continues to be critically weak in most developing countries. Strengthening this link could help to provide fresh stimulus to academic research and re-energize universities and could also be instrumental in the translation of basic research into important commercial products for local use – such as molecular diagnostic tools. This link between academia and private sector is something many countries, even in the industrialized world, have struggled with – countries like France and Germany, for instance, have had limited success in this sphere. Perhaps the country that has most effectively strengthened the interaction between academia and industry is the United States. In 1980, the Bayh-Dole act created incentives for U.S. universities to translate academic research discoveries into innovative commercial products. It granted them ownership of patents arising from federally funded research, as a consequence of which universities have licensed many thousands of patents to the private sector. Although some analysts are skeptical about the impact of the act,[189] others feel this legislation has been instrumental in energizing universities and strengthening the link between academia and the private sector.[190] Over the last few decades there has been a gradual but perceptible change in the role of U.S. universities as "ivory towers" of research to active participants in economic growth.

Conclusion

The processes and initiatives described in this chapter demonstrate some ways in which countries are developing capacity in genomics and biotechnology. There is evidence that mechanisms that foster learning and national systems of innovation can create the scientific capacity countries need to absorb and use biotechnologies to address their heath and development needs.

This report on the contribution of genomics to the MDGs follows those of the UN Science and Technology Task Force, the Inter-Academy Council on Science and Technology Capacity and the UN Commission on Private Sector and Development to outline strategies that developing countries can adopt to develop their science base for health and economic development. It brings greater focus to elements of this strategy, using the example of genomics and related biotechnologies and their potential influence on efforts to achieve the Millennium Development Goals. It describes the need for a global international partnership that can shepherd the process of knowledge-sharing to foster capacity-building in the developing world. It specifies the ways in which genomics can help to address the health-related MDGs, and stresses the need for developing countries to build capacity in genomics in order fully to harness the potential of this exciting and promising field of life sciences. The report echoes the findings of the reports of the UN Science and Technology Task Force, the Inter-Academy Council and the UN Commission on Private Sector and Development.

We present in Box 4.7 the main conclusions from this report.

BOX 4.7 CONCLUSIONS

1. The development gap between developing countries and the industrialized world continues to grow. The international community is beginning to promote science and technology to reduce this gap. The genomics revolution holds tremendous potential to improve health in developing countries and, if harnessed appropriately, could help to reduce the development divide between North and South.

2. Genomics and related biotechnologies can help to achieve the United Nations Millennium Development Goals. Fast, accurate molecular diagnostic devices, safer recombinant vaccines, female-controlled vaginal microbicides and low-cost bioremediation tools are a few of the biotechnologies that can have an impact.

3. Genomics knowledge has the characteristics of a global public good. In order to harness the benefits of genomics for development, the developing world needs, above all, access to genomics knowledge.

4. The promotion of the science of genomics as a global public good and the encouragement of global knowledge flows could best be achieved through international partnerships. A Global Genomics Initiative (GGI) or international partnership of public and private entities from both North and South could catalyze genomics knowledge and learning worldwide.

5. Countries that have genomics capacity are best positioned to take advantage of the genomics revolution to meet their health needs. For the transfer of technologies to be effective and sustainable, they must be accompanied by transfer of science and knowledge. As well, receiving countries must have the capacity to absorb and use the technology.

6. Learning is important for building genomics capacity, and is central to the creation of National Systems of Innovation in biotechnology in developing countries. These countries can strengthen the building blocks of the NSI framework through:

    a. Re-energizing academic institutions and public sector research to strengthen their science base.
    b. Training people and building human capital to use, adapt and innovate biotechnologies.
    c. Encouraging regional and international cooperation to create new channels for knowledge exchange and trade.
    d. Improving the policy environment (including intellectual property laws and regulation) to encourage the building of capacity.
    e. Fostering the growth of the private sector and encouraging it to address local health needs, and strengthening linkages between public and private sectors to create new biotechnology goods and services.

GLOSSARY

A, T, G, C
The four bases of DNA, Adenine, Thymine, Guanine and Cytosine. These are organic molecules made up of carbon, nitrogen, oxygen and hydrogen and they form the 'rungs' of the DNA ladder. Typically, A pairs with T, and G pairs with C.

Amino acid
One of a class of 20 molecules that form the 'building blocks' of proteins in all living organisms. The sequence of amino acids in a protein and hence protein function are determined by the sequence of bases in the corresponding DNA (the genetic code).

Amplification
An increase in the number of copies of a specific DNA fragment; amplification can be in vivo (in an organism, such as bacteria or yeast) or in vitro.
See also: cloning, polymerase chain reaction

Annotation
Addition of pertinent information such as the gene coded for, or the corresponding amino acid sequence or other relevant commentary to raw DNA sequences in databases.
See also: bioinformatics

Antibody
A protein that is produced by the immune system in response to, and counteracts, an antigen.

Antigen
A molecule that triggers an immune response in the body. It induces the formation of antibodies because it is recognized by the immune system as a threat. It may be a foreign (non-native) substance from the environment (such as chemicals) or formed within the body (such as bacterial or viral toxins).

Base
One of the molecules that form DNA and RNA, along with a sugar (either deoxyribose or ribose) and phosphate groups. In DNA, these are adenine, thymine, guanine and cytosine, while in RNA thymine is replaced with uracil.
See also: A, T, G, C, base pair, base sequence, nucleotide

Base pair
Two nitrogenous bases (in DNA, adenine-thymine and guanine-cytosine) held together by weak bonds. The two strands of DNA double helix are held together by the bonds between base pairs (bp).

Bioinformatics
The science of managing, storing, and analyzing large-scale biological data, such as genomic sequences, using advanced computing techniques.

Bioremediation
The use of biological organisms such as plants or microbes to aid in removing hazardous substances from the environment.

Biotechnology
Technology that uses biological organisms and processes in the industrial production of goods and services.

Cancer
Diseases in which abnormal cells divide and grow unchecked. Cancer can spread from its original site to other parts of the body and can be fatal.
See also: hereditary cancer, sporadic cancer

Cell
The basic unit of any living organism that performs biochemical processes of life.
See also: genome, nucleus

Chloroplast
A sub-cellular compartment of a plant cell that captures the energy of sunlight for the production of glucose from carbon dioxide and water.

Chromosome
The self-replicating genetic structure of cells containing cellular DNA. Humans have 23 pairs of chromosomes in each cell of the body.

Clone
An exact copy of biological material such as a DNA segment (e.g., a gene or other region), a whole cell, or a complete organism.

Cloning
The process of using DNA technology to produce multiple, exact copies of biological material. Examples include the cloning of DNA using recombinant technology. A second type of cloning exploits the natural process of cell division to make many copies of an entire cell. The genetic makeup of cloned cells, called a cell line, is identical to the original cell. A third type of cloning produces complete, genetically identical animals such as the first cloned mammal, Dolly.

Cloning vector
DNA molecule originating from a virus, a plasmid, or the cell of a higher organism into which another DNA fragment of appropriate size can be integrated without loss of the vector's capacity for self-replication; vectors introduce foreign DNA into host cells, where the DNA can be reproduced in large quantities. Examples are plasmids, cosmids, and yeast artificial chromosomes.

Cold chain
A complex refrigeration system spanning production to administration, required for most conventional vaccines to preserve them and ensure their effectiveness.

Combinatorial chemistry
A set of easily-automated techniques for producing many different chemical compounds in a short period of time; combinatorial chemistry is commonly used by the pharmaceutical industry for drug discovery and development.

Comparative genomics
The study of genes by comparisons between different organisms such as humans and mice, or the fruit fly. Similarities between the genomes of different organisms can help identify disease genes, or can help in annotation.

Diagnostic
A technique used to diagnose the presence of infection in the body; molecular diagnostics rely on detecting "markers" – molecules that are unique to the pathogen.

DNA (deoxyribonucleic acid)
The molecule that encodes genetic information that encodes proteins and through which this information is passed on from generation to generation. DNA is a double-stranded molecule held together by weak bonds between base pairs of nucleotides. There are four types of nucleotides in DNA (the four building blocks). Each nucleotide consists of a base, a sugar (deoxyribose) and a phosphate group. The four nucleotides in DNA consist of the bases adenine (A), guanine (G), cytosine (C), and thymine (T). In nature, base pairs form only between A and T and between G and C; thus the base sequence of each strand is complementary to and can be deduced from that of its partner.

DNA sequence
The relative order of base pairs, whether in a DNA fragment, gene, chromosome, or an entire genome. The DNA sequence codes for and determines the sequence of amino acids in the corresponding protein.

Double helix
The 'spiral ladder' structure that two linear strands of DNA assume when complementary nucleotides on opposing strands bond together.

Drug target
A biological molecule that interacts with an exogenous molecule (the drug) in such a way that its activity is altered, and consequently, changing an outcome. For example, several pain medications act upon and inhibit an enzyme called cyclooxygenase-2 (COX-2) which triggers the release of prostaglandins that cause inflammation.

ELISA (enzyme-linked immunoabsorbant assay)
Enzyme-linked Immunosorbent Assays (ELISAs) combine the specificity of monoclonal antibodies with the sensitivity of simple enzyme assays, by using antibodies or antigens coupled to an easily-assayed enzyme (an enzyme whose activity can be easily measured). ELISAs can provide a useful measurement of antigen or antibody concentration.

Embryonic stem (ES) cells
An embryonic cell that can replicate indefinitely, transform into other types of cells, and serve as a continuous source of new cells.

Enzyme
A protein that acts as a catalyst, speeding the rate at which a biochemical reaction proceeds but not altering the direction or nature of the reaction.

Escherichia coli
Common bacterium that has been studied intensively by geneticists because of its small genome size, normal lack of pathogenicity, and ease of growth in the laboratory.

Gel electrophoresis
Gel electrophoresis is a method that separates biological macromolecules - either nucleic acids or proteins - on the basis of their size, electric charge, and other physical properties. An electric current is applied across the gel medium and the molecules travel at different speeds through the medium towards the oppositely charged pole. For instance, DNA is negatively charged, and large pieces of DNA move less rapidly through a gel than small pieces. Two-dimensional (2D) gel electrophoresis separates proteins in one direction based on their charge (isoelectric point) and in the second dimension on their molecular mass.

Gene
The fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product (i.e., a protein or RNA molecule).

Gene-gun
A device used for insertion of foreign DNA into plant cells by propulsion. In the original gene-guns (invented by John Sanford, Cornell University) the foreign gene is coated on a pellet that is shot into a cell. The gene inserts itself randomly into the genome of the cell. Newer models are more efficient at gene incorporation.

Gene mapping
Determination of the relative positions of genes on a chromosome and of the distance between them.

Gene product
The biochemical material, either RNA or protein, resulting from expression of a gene.

Gene therapy
An experimental procedure to replace, manipulate, or supplement nonfunctional or malfunctioning genes with healthy genes in living tissue. Typically, a carrier molecule called a vector must be used to deliver the therapeutic gene

to the patient's target cells. Currently, the most commonly used vector is a virus. Viruses are able to introduce their genes into human cells. Scientists have taken advantage of this fact, and genetically engineered viruses to carry therapeutic human DNA instead of disease-causing genes.

Genetic code
The sequence of nucleotides that determines the sequence of amino acids in protein synthesis. Each set of three nucleotides (called codons) codes for one amino-acid in the corresponding protein.

Genetic engineering
The alteration of genetic material of cells or organisms to enable them to make new substances or perform new functions. This is usually achieved by recombinant techniques or by using a gene gun. Also known as genetic modification and gene technology.

Genetic marker
A gene or other identifiable portion of DNA whose inheritance can be followed.

Genetic polymorphism
Difference in DNA sequence among individuals, groups, or populations (e.g., genes for blue eyes versus brown eyes).

Genetic testing
Analyzing an individual's genetic material to determine predisposition to a particular health condition or to confirm a diagnosis of genetic disease.

Genetics
The study of inheritance patterns of specific traits.

Genome
All the genetic material in the chromosomes of an organism.

Genomics
The study of genomes. In our report, we have used genomics to mean: the powerful new wave of health-related life sciences energized by the human genome project and the knowledge and tools it is spawning.

Highly conserved sequence
DNA sequence that is very similar across several different types of organisms.

High-throughput sequencing
A fast method of determining the order of bases in DNA.
See also: sequencing

Immunotherapy
Using elements of the immune system to treat disease, for example, in the development of vaccines.

Intron
DNA sequence that interrupts the protein-coding sequence of a gene; an intron is transcribed into RNA but is cut out of the message before it is translated into protein.
See also: exon

Kilobase
Unit of length for DNA fragments equal to 1000 nucleotides.

Knockout
Deactivation of specific genes; used in laboratory organisms to study gene function. A knockout mouse can be studied for the effects caused by the inactivation of a particular gene.

Mapping
See: gene mapping, linkage map, physical map

Mass spectrometry
A technique used to identify chemicals in a substance by

their mass and charge. One application has been in proteomics to determine the amino acid sequence of proteins.

Megabase
Unit of length for DNA fragments equal to 1 million nucleotides.

Messenger RNA (mRNA)
RNA that is encoded from DNA and serves as a template for protein synthesis.

Microarray
Set of miniaturized chemical reaction areas (wells) that may also be used to test DNA fragments, antibodies, or proteins.

Microbicide
A substance that can reduce or prevent infection. Vaginal microbicides can prevent sexually-transmitted infection and may or may not act as a contraceptive.

Microinjection
A technique for injecting DNA into animal cells with a tiny needle.

Mitochondria
Organelles in cells that convert food into energy.

Model organisms
A laboratory animal or other organism useful for research.

Molecular biology
The study of the structure, function, and makeup of biologically important molecules.

Molecular pharming
The development of transgenic plants or animals to produce human proteins for medical use.

Molecular genetics
The study of molecules important in biological inheritance.

Molecular medicine
The treatment of injury or disease at the molecular level. Examples include the use of DNA-based diagnostic tests or medicine derived from DNA sequence information.

Monoclonal antibodies
Antibodies of exceptional purity and specificity that are able to recognize and bind to a specific antigen. They are derived from the progeny of a single immune cell.

Multiplexing
A laboratory approach that performs multiple sets of reactions simultaneously; this increases speed and throughput.

Mutagen
An agent that causes a permanent genetic change in a cell. Does not include changes occurring during normal genetic recombination.

Mutation
Any change in normal DNA sequence.

Nitrogenous base
A nitrogen-containing molecule with the chemical properties of a base (such as ammonia). DNA contains the nitrogenous bases adenine (A), guanine (G), cytosine (C), and thymine (T).

Non-communicable diseases
Generally refers to chronic diseases that cannot be transmitted horizontally from person to person, as opposed to communicable or infectious diseases such as malaria or tuberculosis. They may or may not have a hereditary component (and therefore could be transmitted vertically from one generation to the next). Examples include cancer, diabetes and heart disease.

Nucleic acid
A large molecule composed of nucleotide subunits. DNA and RNA are nucleic acids.
See also: DNA

Nucleotide
A subunit of DNA or RNA consisting of a nitrogenous base (adenine, guanine, thymine, or cytosine in DNA; adenine, guanine, uracil, or cytosine in RNA), a phosphate molecule, and a sugar molecule (deoxyribose in DNA and ribose in RNA). Thousands of nucleotides are linked to form a DNA or RNA molecule.

Nucleus
The cellular organelle in eukaryotic cells that contains most of the genetic material.

Peptide
Two or more amino acids joined by a bond called a "peptide bond." Proteins are made up of peptide chains.

Pharmacogenomics
The study of the interaction of an individual's genetic makeup and response to a drug.

Phytoremediation
The use of natural and genetically-engineered plants for cleaning up environmental pollution; a sub-field of bioremediation.

Plantibodies
Antibodies produced by genetically-engineered plants. They are low-cost alternatives to monoclonal antibodies produced in mammalian culture, but suffer from some disadvantages.

Plasmid
Bacterial cells contain independently replicating circular DNA molecules, distinct from the normal bacterial genome and nonessential for cell survival under normal conditions. Plasmids are used to insert foreign genes into bacterial cells. As the bacterial cells replicate, the foreign DNA multiplies. A number of artificially constructed plasmids are used as cloning vectors.

Polymerase chain reaction (PCR)
A method for making several copies of a DNA base sequence. PCR also can be used to detect the existence of the defined sequence in a DNA sample, such as in forensics.

Polymerase, DNA or RNA
Enzyme that catalyzes the synthesis of nucleic acids on preexisting nucleic acid templates, assembling RNA from ribonucleotides or DNA from deoxyribonucleotides.

Probe
A small molecule that is able to bind to another molecule in a sample, such as particular sequence of DNA, or a particular protein. The probe is labeled with another molecule in order to make it detectable. For example, a fluorescent probe lights up and can be detected when it binds its complementary partner.

Protein
A macromolecule composed of one or more chains of amino acids in a specific order; the order is determined by the base sequence of nucleotides in the gene that codes for the protein. Proteins are required for the structure, function, and regulation of the body's cells, tissues, and organs; and each protein has unique functions. Examples are hormones, enzymes, and antibodies.

Proteome
All the proteins expressed by a cell or a tissue at a particular time and under specific conditions. Unlike the genome, which is constant and identical in all the body cells, the proteome changes constantly depending on the requirements of the organism at a given time.

Proteomics
The study of the proteome.

Recombinant DNA molecules
A combination of DNA molecules of different origin joined using recombinant DNA technologies *(see below)*.

Recombinant DNA technology
Any procedure for combining DNA from two or more different sources. It makes use of restriction enzymes to cut and introduce foreign DNA into a plasmid or other vector. Under appropriate conditions, a recombinant DNA molecule can enter a cell and replicate there (using, for instance, a gene gun). The function of the isolated foreign DNA can be studied using this technique, or the expressed protein can be harvested, as in molecular pharming.

Restriction enzyme
Bacterial enzymes used in recombinant DNA technology to cut DNA for insertion of foreign DNA. (Their purpose in nature is to protect bacteria against intruding DNA from other organisms). They are very specific, recognizing short, specific nucleotide sequences in DNA molecules and cutting at specific points within these sequences. Bacteria contain over 400 such enzymes that recognize and cut more than 100 different DNA sequences. Once the DNA is cut and the foreign DNA introduced, the enzyme ligase seals the ends to make a continuous DNA molecule.

Ribose
A five-carbon sugar that is a component of RNA. Deoxyribose is the corresponding sugar in DNA. The presence of an extra O atom in RNA makes this molecule more reactive than DNA, which is why DNA is the form in which hereditary information is stored and RNA is the form in which information is decoded to form proteins.

RNA (Ribonucleic acid)
A biological macromolecule found in the nucleus and cytoplasm of cells; it plays an important role in protein synthesis and other chemical activities of the cell. The structure of RNA is similar to that of DNA. It is also made up of nitrogenous bases: adenine, uracil, guanine and cytosine. There are many kinds of RNA molecules, including messenger RNA, transfer RNA, ribosomal RNA, and other small RNAs, each serving a different purpose.

Sanger sequencing
A widely used method of determining the order of bases in DNA.

Sequencing
Determination of the order of nucleotides (base sequences) in a DNA or RNA molecule or the order of amino acids in a protein.

Shotgun sequencing
Sequencing method that involves randomly sequenced cloned pieces of the genome, with no foreknowledge of where the piece originally came from. This can be contrasted with "directed" strategies, in which pieces of DNA from known chromosomal locations are sequenced. Because there are advantages to both strategies, researchers have used both random (or shotgun) and directed strategies in combination to sequence genomes.

Single nucleotide polymorphism (SNP)
DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered.

Stem cell
Undifferentiated, primitive cells in the bone marrow that have the ability both to multiply and to differentiate into specific blood cells.

Structural genomics
The effort to determine the 3D structures of large numbers of proteins using both experimental techniques and computer simulation

STI
Sexually transmitted infection – diseases transmitted primarily through sexual intercourse (such as HIV/AIDS, Chlamydia, gonorrhea).

Transgenic
A genetically-engineered organism in which DNA has been artificially introduced and incorporated into the organism's germ line.

Therapeutic
A substance used to treat a disease after diagnosis.

Vaccine
A pathogen-derived substance containing antigens that stimulates the immune system to produce antibodies but does not cause infection.

Vector
An agent, such as a virus or a plasmid that can carry a foreign gene into a cell. Can also refer to an organism that transfers a pathogen to a host (e.g. mosquitoes act as a vector for *Plasmodium falciparum* which causes malaria).

Virus
A non-cellular biological entity that can reproduce only within a host cell. Viruses consist of nucleic acid covered by protein; some animal viruses are also surrounded by membrane. Inside the infected cell, the virus uses the synthetic capability of the host to produce progeny virus.

REFERENCES

1. WHO (1999). World Health Report 1999 – Making a Difference. (Geneva).

2. Annan K (2003). A Challenge to the World's Scientists. *Science.* 299: 1485.

3. In this report, we use the term genomics to describe the powerful new wave of health-related life sciences energized by the human genome project and the knowledge and tools it is spawning.

4. UN Millennium Development Goals. (http://www.un.org/millenniumgoals/).

5. Science & Technology Task Force Interim Report. (www.unmillenniumproject.org/documents/tf10interim.pdf).

6. United Nations Development Programme (2001). Human Development Report 2001: *Making New Technologies Work for Human Development*. (New York: Oxford University Press).

7. The increase in life expectancy in Europe started prior to the introduction of vaccines and antibiotics; it was driven largely by improvements in sanitation and diets. Chen L (1983). Child survival: Levels, trends, and determinants in *Determinants of Fertility in Developing Countries: Supply and Demand for Children, Volume One*.RA Bulatao & RD Lee (Eds.) (New York: Academic Press).

8. Wang J *et al* (1999). Measuring Country Performance on Health: Selected Indicators for 115 Countries. *Health, Nutrition, and Population Series.* (Washington, DC: World Bank).

9. Wagner C. *et al.* (2001). Science and Technology Collaboration: Building Capacity in Developing Countries. (Washington D.C.: The RAND Corporation).

10. Organisation for Economic Co-Operation and Development (1999). Managing National Innovation Systems. *OECD Science and Information Technology.* 1999(6): 1-112.

11. Inter-Academy Council (2004). Inventing a Better Future: A Strategy for Building Worldwide Capacities in Science and Technology http://www.interacademycouncil.net/report.asp?id=6258

12. USAID (2002). Life Expectancy Will Drop Worldwide Due To AIDS. (http://www.usaid.gov/press/releases/2002/pr020708.html).

13. WHO (2001). Macroeconomics and Health: Investing in Health for Economic Development Report of the Commission on Macroeconomics and Health. (http://www3.who.int/whosis/menu.cfm?path=whosis,cmh&language=english).

14. Barro R & X Sala-I-Martin (1995). Economic Growth. (New York: McGraw-Hill)

15. Bloom DE & JD Sachs (1998). Geography, Demography and Economic Growth in Africa. *Brookings Papers on Economic Activity.* 2: 207-295

16. Bhargava A *et al.* (2001). Modeling the effects of health on economic growth. *J. of Health Economics.* 20: 423-440.

17. Global Forum Health Research (2002). 10/90 Report on Health Research. (Geneva: Global Forum for Health Research).

18. WHO (2002). Genomics and World Health: Report of the Advisory Committee on Health Research. (Geneva).

19a. Bourgaize D *et al.* (1999). Biotechnology: Demystifying the Concepts. (Reading, MA: Addison-Wesley Publishing Company)

19b. Morange M (1998). A History of Molecular Biology. (Cambridge, MA: Harvard University Press).

20. Billings PKS (2001). What is the human genome? JF Mattei (Ed.). *The Human Genome.* (Strasbourg: Council of Europe Publishing).

21a. Venter JC *et al.* (2001). The sequence of the human genome. *Science*. 291: 1304-1351

21b. International Human Genome Sequencing Consortium (2001). Initial sequencing and analysis of the human genome. *Nature.* 409: 860-921.

22. Lacadena JR (2001). An ethical code for human genetics. JF Mattei (Ed.) *The Human Genome.* (Strasbourg: Council of Europe Publishing).

23. Thomas SM (1999). Genomics and intellectual property rights. *Drug Discovery Today.* 4(3): 134-138

24. Luscombe NM *et al.* (2001). What is bioinformatics? A proposed definition and overview of the field. *Methods Inf. Med.* 40(4): 346-358.

25. Fleischmann RD *et al.* (1995). Whole-genome random sequencing and assembly of *Haemophilus influenzae* Rd. *Science.* 269(5223): 496-512.

26. Gardner MJ *et al.* (2002). Genome sequence of the human malaria parasite *Plasmodium falciparum*. *Nature*. 419: 498-511

27. Collins FS (1999). Shauttuck lecture - Medical and societal consequences of the human genome project. *NEJM.* 341(1): 28-37.

28. Human Genome Project. (http://www.genome.gov).

29. Ernst & Young (2001). Focus on Fundamentals: The Biotechnology Report 15th Annual Review. (United Kingdom: Ernst & Young LLP).

30. Carr K (1999). Cuban biotechnology treads a lonely path. *Nature.* 398: A22-A23.

31. Commission on the Private Sector & Development (2004). Unleashing Entrepreneurship: Making Business Work for the Poor. United Nations, New York, NY

32. Singer PA & AS Daar (2001). Harnessing genomics and biotechnology to improve global health equity. *Science.* 294: 87–89.

33. Varmus H *et al.* (2003). Grand Challenges in Global Health. *Science*; 302(5644): 398-9.

34. Acharya T *et al.* (2003). Biotechnology and the UN's Millennium Development Goals. *Nat Biotechnol.* 21(12):1434-6

35. Daar AS *et al.* (2002). Top 10 biotechnologies for improving health in developing countries. *Nat. Gen.* 32: 229-232.

36. UNFPA (2001). Understanding the Causes of Maternal Deaths. (Distance Learning Pilot Course).

37. WHO (1998). Fact Sheet 178: Reducing mortality from major killers of children. (http://www.who.int/inf-fs/en/fact178.html).

38. WHO (2000). Backgrounder No. 1: HIV, TB and Malaria—Three Major Infectious Disease Threats. (http://www.who.int/inf-fs/en/back001.html).

39. Global Fund to Fight AIDS, TB & Malaria. (http://www.globalfundatm.org).

40. World Health Organization (1996) Fact Sheet No. 112 - Water and Sanitation http://www.lifewater.org/fact112.htm

41. Adler M & E Ziglio (1996). Gazing into the Oracle: The Delphi Method and its Implications to Social Policy and Public Health. (London: Jessica Kingsley Publishers).

42. Louie M *et al.* (2000). The role of DNA amplification technology in the diagnosis of infectious disease. *CMAJ.* 163(3): 301-309.

43. Harris E *et al.* (1996). Detection of *Trypanosoma brucei* spp in human blood by a nonradioactive branched DNA-based technique. *J Clin Microbiol.* 34(10): 2401-7.

44. Beck IA *et al.* (2001). Simple, sensitive, and specific detection of Human Immunodeficiency Virus Type 1 Subtype B DNA in dried blood samples for diagnosis of infants in the field. *J Clin Microbiol.* 39(1): 29-33.

45. Harris E *et al.* (1998). Single-step multiplex PCR assay for characterization of New World *Leishmania* complexes. *J Clin Microbiol.* 36(7): 1989-1995.

46. Park SJ *et al.* (2002). Array-based electrical detection of DNA with nanoparticle probes. *Science* 295(5559): 1503-1506.

47. OptiMAL. (http://www.malariatest.com/).

48. Palmer CJ *et al.* (1998). Evaluation of the OptiMAL test for rapid diagnosis of *Plasmodium vivax* and *Plasmodium falciparum* malaria. *J Clin Microbiol.* 36(1): 203-206.

49. PATH – Program for Appropriate Technology in Health. (www.path.org).

50. Arai H *et al.* (1999). Evaluation of a rapid immunochromatographic test for detection of antibiodies to human immunodeficiency virus. *J Clin Micriobiol.* 37(2): 367-370.

51. Quidel. (http://www.quidel.com/Products/product-disp.php?prod=95&section=pro).

52. Porterfield JS & JO Tobin (1984). Viral and bacterial infectious diseases. *Br Med Bull.* 40(3): 283-90.

53. Daniell H *et al.* (2001). Medical molecular farming: production of antibodies, biopharmaceuticals and edible vaccines in plants. *Trends Plant Sci.* 6(5): 219-226.

54. Epicyte Website. Epicyte Products in Development. (http://www.epicyte.com/products/products1.html).

55. AIDS Education Global Information System. (http://www.aegis.com/news/bw/2001/BW010605.html).

56. Ewer K *et al.* (2003). Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak. *Lancet.* 361(9364): 1168-1173.

57. Widdus R (1999). The potential to control or eradicate infectious diseases through immunisation. *Vaccine.* 17(2): S6-12.

58. Walmsley AM & CJ Arntzen (2000). Plants for delivery of edible vaccines. *Curr Opin Biotechnol*. 11(2): 126-129.

59. Richter LJ *et al.* (2000). Production of hepatitis B surface antigen in transgenic plants for oral immunization. *Nat. Biotech*. 18(11): 1167-1171.

60a. Webster DE *et al.* (2002). Successful boosting of a DNA measles immunization with an oral plant-derived measles virus vaccine. *J Virol*. 76(15): 7910-7912

60b. Mason HS *et al.* (1996). Expression of Norwalk virus capsid protein in transgenic tobacco and potato and its oral immunogenicity in mice. *Proc Natl Acad Sci*. 93(11): 5335-5340

60c. Jani D *et al.* (2002). Expression of cholera toxin B subunit in transgenic tomato plants. *Transgenic Res.* 11(5): 447-54.

61. Pipeline Project. Table of Vaccine Trials. (http://chi.ucsf.edu/vaccines?page=vc-03-00).

62. International AIDS Vaccine Initiative (http://www.iavi.org/iavireport/0103/trialswatch.htm).

63. Gp120 (glycoprotein – molecular weight 120,000) is the main surface antigen (Ag) and is what binds to human cells. Several studies have shown that only long-term nonprogressors mount effective anti-gp120 antibody responses making Gp120 a promising vaccine candidate.

64. Belshe RB *et al.* (2001). Safety and immunogenicity of a canarypox-vectored human immunodeficiency virus Type 1 vaccine with or without gp120: a phase 2 study in higher- and lower-risk volunteers. *J Infect Dis*. 183(9): 1343-52.

65. Voss G *et al.* (2003). Prevention of disease induced by a partially heterologous AIDS virus in rhesus monkeys by using an adjuvanted multicomponent protein vaccine. *J Virol*. 77(2): 1049-1058.

66. Vaxgen. (www.vaxgen.com).

67. National Institutes of Health. Press Release: New HIV Vaccine Holds Promise of Global Effectiveness. (http://www.nih.gov/news/pr/nov2002/niaid-13.htm).

68. Klausner *et al.* (2003). The Need for a Global HIV Vaccine Enterprise. *Science*. 300: 2036-2039.

69. Bojang KA *et al.* (2001). Efficacy of RTS, S/AS02 malaria vaccine against *Plasmodium falciparum* infection in semi-immune adult men in The Gambia: a randomised trial. *Lancet*. 358(9297): 1927-1934.

70. Malaria Vaccine Initiative (2001). Press Release: Clinical trials of advanced malaria vaccine candidate expand to Mozambique. (http://www.malariavaccine.org/files/MVI-GSK-CISM-011205.htm).

71. Stowers AW *et al.* (2002). A recombinant vaccine expressed in the milk of transgenic mice protects Aotus monkeys from a lethal challenges with *Plasmodium falciparum*. *Proc Natl Acad Sci*. 99(1): 339-344.

72. Carol AN & KA Sacksteder (2002). New tuberculosis vaccine development. *Expert Opinion on Biological Therapy*. 2(7): 741-749.

73. Coler RN *et al.* (2001). Vaccination with the T cell antigen Mtb 8.4 protects against challenge with *Mycobacterium tuberculosis*. *J Immunol.* 166(10): 6227-6235.

74. Kapusta J *et al.* (1999). A plant-derived edible vaccine against hepatitis B virus. *FASEB.* 13(13): 1796-1799.

75. Chikwamba R *et al.* (2002). A functional antigen in a practical crop: LT-B producing maize protects mice against Escherichia coli heat labile enterotoxin (LT) and cholera toxin (CT). *Transgenic Res*. 11(5): 479-93.

76. Kane A *et al.* (1999). Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: model-based regional estimates. *Bull World Health Organ*. 77(10): 801-807.

77. WHO – Communicable Disease Surveillance & Response – Drug Resistance http://www.who.int/csr/drugresist/en/

78. Korkusuz F *et al.* (2001). *In vivo* response to biodegradable controlled antibiotic release systems. *J Biomed Mater Res*. 55(2): 217-228.

79. Moynihan JS *et al.* (2002). Enhanced immunogenicity of a hepatitis B virus peptide vaccine using oligosaccharide ester derivative microparticles. *Vaccine*. 20(13-14): 1870-1876.

80. Harsch IA *et al.* (2001). Syringe, pen, inhaler—the evolution of insulin therapy. *Med Sci Monit*. 7(4): 833-836.

81. Fernandez de Castro J *et al.* (1997). La vacunacion antisarampionosa en Mexico por el metodo de aerosol. *Salud Publica Mex*. 39(1): 53-60.

82. Biospace News (2001). Crucell NV (CRXL) and Vaxin, Inc. to jointly develop new types of vaccines which make injections obsolete. (Accessed December 2002; see http://www.biospace.com/news_story.cfm?StoryID=5491204&full=1).

83. Powderject. (www.powderject.com).

84. Ocean Arks International. (http://www.oceanarks.org/about/intro/).

85. Exxon Valdez Oil-spill Council (http://www.oilspill.state.ak.us/facts/qanda.html).

86. Pritchard PH & CF Costa (1991). EPA Alaska oil spill bioremediation project. *Environ Sci Technol*. 25(3): 372-379.

87. Weider RK (1989). A Survey of constructed wetlands for acid coal mine drainage treatment in the eastern US. *Wetlands.* 9: 299-312.

88. Brim H *et al.* (2000). Engineering *Deinococcus radiodurans* for metal remediation in radioactive mixed waste environments. *Nat Biotechnol*. 18(1): 85-90.

89. International Development Research Centre (IDRC) *Coconuts and the Community - Malaria Control in Peru* http://web.idrc.ca/en/ev-26937-201-1-DO_TOPIC.html

90. WHO (2000). Press Release: 8 September. Researchers warn of impending disaster from mass arsenic poisoning. (http://www.who.int/inf-pr-2000/en/pr2000-55.html).

91. Santini J *et al* (2000). A new chemolithoautotrophic arsenite-oxidizing bacterium isolated from a gold

mine: phylogenetic, physiological and preliminary biochemical studies. *Appl Environ Micriobiol*. 66(1): 92-97.

92. Ma LQ *et al.* (2001). A fern that hyperaccumulates arsenic. *Nature* 409: 579.

93. Sanger F *et al* (1977). Nucleotide sequence of bacteriophage phi X174 DNA. *Nature*. 165: 687-695.

94. Loferer H *et al.* (2000). Integrated bacterial genomics for the discovery of novel antimicrobials. *Drug Discovery Today*. 5(3): 107-14.

95. Jomaa H *et al.* (1999). Inhibitors of the nonmavalonate pathway of isoprenoid biosynthesis as antimalarial drugs. *Science.* 285(5433): 1573-76.

96. Missinou MA *et al.* (2002). Fosmidomycin for malaria. *Lancet.* 360(9349): 1941-1942.

97. Balter M (2001). Malarial research: Sequencing set for dreaded mosquito. *Science,* 291(5510): 1873.

98. Land KM (2003). The mosquito genome: perspectives and possibilities. *Trends Parasitol.*;19(3):103-5

99. Cowman A (2001). Functional analysis of drug resistance in *Plasmodium falciparum* in the postgenomic era. *Int J Parasitol.* 31(9): 871-878.

100. Pizza M *et al* (2000). Identification of vaccine candidates against serogroup B meningococcus by whole-genome sequencing. *Science.* 287(5459): 1816-1820.

101. World Bank (1993). World Development Report 1993: Investing in Health. (Oxford: Oxford University Press).

102. WHO (2000). Fact Sheet 249: Women and Sexually Transmitted Infections. (http://www.who.int/inf-fs/en/fact249.html).

103. Forbes A & L Heise (2000). What's up with nonoxynol-9? *Reprod Health Matters.* 8(16): 156-159.

104. Zeitlin L *et al.* (1999). Using monoclonal antibodies to prevent mucosal transmission of epidemic infectious diseases. *Emerg Infect. Dis.* 5(1): 54-64.

105. Population Council. (http://www.popcouncil.org/biomed/candidate.html).

106. Van De Wijgert J (2001). Phase 1 trial of the topical microbicide BufferGel: safety results from four international sites. *J Acquir Immune Defic Syndr.* 26(1): 21-27.

107. Herold *et al.* (2002) Mandelic acid condensation polymer: novel candidate microbicide for prevention of human immunodeficiency virus and herpes simplex virus entry. *J Virol.* Nov;76(22):11236-44.

108. Blakeslee D (1998). Blocking HIV transmission the natural way: 2 new ideas. *JAMA HIV/AIDS Information Centre Special Report*.

109. Boyd MD (1997). Discovery of cyanovirin-N, a novel human immunodeficiency virus-inactivating protein that binds viral surface envelope glycoprotein gp120: potential applications to microbicide development. *Antimicrob Agents Chemother.* 41(7): 1521-30.

110. Chang TL *et al.* (2003). Inhibition of HIV infectivity by a natural human isolate of *Lactobacillus jensenii* engineered to express functional two-domain CD4. *Proc Natl Acad Sci*;100(20):11672-7

111. Yuan H *et al.* (2001). Antibacterial vaccine design using genomics and proteomics. *Trends Biotechnol.* 19(5): 181-188

112. Fletcher MA (2001). Vaccine candidates in STD. *Int Journal STD AIDS.* 12(7): 419-422.

113. NCBI. Growth of GenBank. (http://www.ncbi.nih.gov/Genbank/genbankstats.html).

114. Swiss-Prot. (http://ca/expasy.org/sprot/).

115. Structure. (www.ncbi/nih/gov/Structure).

116. Anopheles Database. (http://skonops.imbb.forth.gr/AnoBase/).

117. S-star. (http://s-star.org).

118. Avison MB (2004) Comparative genomics: digging for data. *Methods Mol Biol.*;266:47-69

119. Lyall A (1996). Bioinformatics in the pharmaceutical industry. *Trends Biotech.* 14(8): 308-312.

120. Terstappen GC & A Reggiani (2001). *In silico* research in drug discovery. *Trends Pharmacol Sci.* 22(1):23-26.

121. Grandi G (2001). Antibacterial vaccine design using genomics and proteomics. *Trends Biotech.* 19(5):181-8.

122. Payne DJ (2001). Bacterial fatty-acid biosynthesis: a genomics-driven target for antibacterial drug discovery. *Drug Discov Today.* 6(10): 537-44.

123. World Health Organization – Vitamin A http://www.who.int/vaccines-diseases/en/vitamina/science/sci02.shtml

124. Ye X *et al.* (2000). Engineering the provitamin A (b-carotene) biosynthetic pathway into (carotenoid-free) rice endosperm. *Science* 287(5451): 303-305.

125. ß-Carotene, which is naturally converted by the body into Vitamin A, is five times less toxic than Vitamin A in high doses.

126. Potrykus I (2001). Golden rice and beyond. *Plant Physiol.* 125(3): 1157-1161.

127. Schiermeier Q (2001). Designer rice to combat diet deficiencies makes its debut. *Nature.* 409: 551.

128. Chakraborty S *et al.* (2000). Increased nutritive value of transgenic potato by expressing a nonallergenic seed of albumin gene from *Amaranthus hypochodriaccus. Proc Natl Acad Sci USA.* 97(7): 3724-3729.

129. Coghlan A (2003). 'Protato' to feed India's poor. *New Scientist.* 177(2376): 7.

130. Jain AK & CL Nessler (2000). Metabolic engineering of an alternative pathway for ascorbic acid biosynthesis in plants. *Molecular Breeding.* 6(1):73-8.

131. Bagchi K & S Puri (1998). Free radicals and antioxidants in health and disease. *Eastern Mediterranean Health Jl.* 4(2): 350-360.

132. Schubert D (2002). A different perspective of GM food. *Nat Biotech.* 20: 969.

133a. Beachy R et al. (2002). Divergent perspectives on GM food. Nat Biotech. 20: 1195-6

133b. Avery A (2002). Divergent perspectives on GM food. *Nat Biotech.* 20: 1196.

134. WHO (1999). World Health Report 2000 – Health Systems: Improving Performance. (Geneva).

135. Breekveldt J & J Jongerden (1998). Transgenic animals in pharmaceutical production. *Biotechnol Dev Monitor.* 36:19-22.

136. Bakker H *et al.* (2001). Galactose-extended glycans of antibodies produced by transgenic plants. *Proc. Natl. Acad. Sci.* 98(5): 2899-2904.

137. Anonymous (2002). Biocon and Shanta JV for human insulin. *The Hindu* (http://www.hinduonnet.com/2002/04/11/stories/2002041101601800.htm).

138. Martin VJJ *et al.* (2003). Engineering a mevalonate pathway in *Escherichia Coli* for production of terpenoids. *Nat. Biotech.* 21: 796-802.

139. Graven A *et al.* (2001). Combinatorial library of peptide isosters based on Diels-Alder reactions: identification of novel inhibitors against a recombinant cysteine protease from Leishmania mexicana. *J Comb Chem.* 3(5):441-52.

140. Nicolaou KC *et al.* (2001). Synthesis and biological evaluation of vancomycin dimers with potent activity against vancomycin-resistant bacteria: target-accelerated combinatorial synthesis. *Chemistry.* 7(17): 3824-3843.

141. Hoekstra WJ *et al.* (1999). Potent, orally available GPIIb/Iia antagonists containing a nipecotic acid subunit. Structure-activity studies leading to the discovery of RWJ-53308. *J Med Chem.* 42(25): 5254-65.

142. Miertus S & G Fassina (1999). Combinatorial Chemistry and Technology. (New York: Marcel Dekker Inc.).

143. Annan K (2004). Science for all Nations. *Science.* 303; 925.

144. By governance we mean processes and institutions by which we make decisions concerning public life, economic and social development.

145. Thorsteinsdóttir H *et al.* (2003). Genomics knowledge. RD Smith et al (Eds.). *Global Public Goods for Health: a health economic and public health perspective.* (Oxford University Press).

146. The concepts presented here were developed in close collaboration with Richard Smith, Senior Lecturer at the School of Health Policy & Practice in the University of East Anglia.

147. Woodward D & RD Smith (2003). Global public goods for health: Concept and policy issues. In: RD Smith *et al.* (eds.). *Global Public Goods for Health: a health economic and public health perspective* (Oxford University Press).

148. Stiglitz JE (1999). Knowledge as a global public good. I Grunberg *et al* (Eds.). *Global public goods: international cooperation in the 21st century.* (New York: Oxford University Press) 308-325.

149. UNESCO (1997). Universal Declaration on the Human Genome and Human Rights. (Geneva).

150. Smith G & A Zweig (2000). Biotechnology and the state of global negotiations. Centre for Global Studies, University of Victoria. (http://www.globalcentres.org/html/docs/Biotech.pdf).

151. Rischard JF (2001). High Noon: We need new approaches to global problem-solving, fast. *J. of Int. Econ. Law.* 4(3): 507-525.

152. Annan K (2000). We the Peoples: The Role of the United Nations in the 21st Century. (Geneva: United Nations Millennium Report).

153. Reinecke WH & FM Deng (2000). Critical choices: the United Nations, networks, and the future of global governance. (http://www.gppi.net/cms/public/a1224f819197be4e797e38bb6b6ba511critical%20choices%20final.pdf).

154. Kickbusch I (2000). The development of international health policies – accountability intact? *Soc. Sci. Med*. 51: 979-989.

155a. Solow R (1957). "Technical Change and the Aggregate Production Function." *Review of Economics and Statistics*, 39:312-320

155b Freeman C (1974). The Economics of Industrial Innovation, New York. Penguin Books

155c. Abramowitz M (1977). "Rapid Growth Potential and its Realisation: The Experience of Capitalist Economies in the Postwar Period", E. Malinvaud (ed.) *Economic Growth and Resources*, Proceedings of the 5th World Congress of the International Economic Association, Vol. 1, Tokyo.

156. Westphal L *et al.* (1985). "Reflections on the Republic of Korea's Acquisition of Technological Capability" in N. Rosenberg & C. Frishtak (eds.), *International Technology Transfer: Concepts, measures and Comparisons*, N.Y.: Praeger, pp. 167-221;

157. Lall S (2000). "Technological change and Industrialization in the Asian Newly Industrializing Economies: Achievements and Challenges" in Kim L & Nelson R (eds.) *Technology, learning and Innovation Experiences of Newly Industrializing Economies*, U.K., Cambridge University Press, pp. 13-66

158. Katz, J. (1985) "Domestic Technological Innovations and Dynamic Comparative Advantages: Further Reflections on a Comparative Case-Study Program" in N. Rosenberg & C.Frischtak (eds.) *International Technology transfer: Concepts, Measures, and Comparisons,* N.Y.:Praeger, pp.127-166.

159. Skolnikoff E (1993). The Elusive Transformation: Science. Technology, and the Evolution of International Politics. Princeton University Press.

160. Kryl D (2001). Environmental and Industrial Biotechnology in Developing Countries. (http://www.ejbiotechnology.info/content/vol4/issue3/issues/03/).

161. Pavitt K (2001). Public Policies to Support Basic Research: What Can the Rest of the World Learn from US Theory and Practice? (And What They Should Not Learn). *Industrial and Corporate Change.* 10: 761.

162. Callon M (1994). "Is science a public good?" Fifth Mullins Lecture, Virginia Polytechnic Institute. *Science, Technology and Human Values, 19*(4), 395-424

163. Acharya R (1999). The Emergence and Growth of Biotechnology: Experiences in Industralised and Developing Countries (Cheltenham, England: Edward Elgar Publishers).

164a. Freeman C (1988). "Japan: An New National System of Innovation". In Dosi G, Freeman C, Nelson R, Silverberg G and Soete L. Technical Change and Economic Theory. London and New York: Pinter

164b. Lundvall BA (1992). National System of Innovation: Toward a theory of innovation and interactive learning. (London: Pinter Publishers).

164c. Nelson R (1993). Nelson: National Innovation Systems: A Comparative Analysis; Oxford University Press, New York.

165. Edquist C (1997). (ed.). Systems of Innovation: Technologies, Institutions, and Organizations. London: Pinter.

166. Niosi J (1999). The internationalization of industrial R&D: From technology transfer to the learning organization. *Research Policy* 28:107–17.

167. Arocena R & J Sutz (2000). Looking at National Systems of Innovation from the South. *Industry and Innovation,* Volume 7, Number 1, 55–75.

168. Intarakamnerd P *et al.* (2001). National Innovation Systems in Less Successful Developing Countries: The Case of Thailand. Paper presented at the DRUID Conference, Aalborg, Denmark, June 12-15.

169. Lundvall BA *et al.* (2002). National systems of production, innovation and competence building. *Research Policy* 2002 31(2): 213-231.

170. Ernst D *et al.* (1998). "Technological capabilities in the context of export-led growth: a conceptual framework" in Ernst, Ganiatsos & Mytelka (eds.) *Technological Capabilities and Export Success in Asia*, U.K.: Routledge, pp. 5-45

171. Canadian Program on Genomics and Global Health. (www.geneticsethics.net).

172. Juma C & V Konde (2002). Industrial applications for biotechnology: opportunities for developing countries. *Environment*, July-August v44 i6 p22(15)

173. TDR Initiative. (http://www.who.int/tdr/grants/awards/bioinformatics-10-01.htm).

174. Oduola A *et al.* (2002). Genomics and bioinformatics for tropical diseases. *TDR Newsletter.* 68. (http://www.who.int/tdr/publications/tdrnews/news68/bioinformatics.htm).

175. Sustainable Sciences Institute. (http://www.ssilink.org/).

176. Orellana C (2004). Chile launches policy to boost biotech. *Nat Biotech* 22:1;7-8

177. Elderhorst M (1994). Will Cuba's Biotechnology Capacity Survive the Socio-economic Crisis? *Biotechnology and Development Monitor*, No. 20, p. 11-13/22.

178. http://www.utoronto.ca/jcb/genomics/html/ACTS_synthesis.htm

179. Acharya T *et al.* (2004). Harnessing genomics to improve health in India (for the Indian Genome Policy Forum). *Health Res. Pol. Syst.*, 2:1.

180. Abdur Rab M, *personal communication*

181. INK - Knowledge Societies - Information Technology for Sustainable Development Robin Mansell and Uta Wehn, Editors Oxford University Press, ISBN 0-19-829410-7, March 1998

182. South Centre Bulletin 77 (2004). (http://www.southcentre.org/info/southbulletin/bulletin77/bulletin77-03.htm#TopOfPage).

183. Centre for the Management of Intellectual Property in Health Research and Development (MIHR) (www.mihr.org).

184. Saha R *et al.* (2004). Building a "Cottage Industry" for Health (and Wealth): The New Framework for IP Management in India. *IP Strategy Today*, issue 10.

185. United Nations University Institute for Advanced Studies - Traditional Knowledge and Intellectual Property Rights (http://www.ias.unu.edu/research/tkipr.cfm).

186. Domingo-Morales MC (2002). Senior Planning Officer of the Philippine Department of Agriculture, Report Presented to the Seminar on Traditional Knowledge, 3-5 April, New Delhi, India. (http://r0.unctad.org/trade_env/test1/meetings/delhi/Countriestext/Philipinestext.doc)

187. Asian Health Newsletter, "India," April 24th 2001, page 2.

188. Egoli BIO Life Sciences Incubator http://www.egolibio.co.za/pages/about.htm

189. Mowery D *et al.* (2001). The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act of 1980. *Research Policy* 30:99-119

190. Mehta S (2004). The emerging role of academia in commercializing innovation *Nat Biotech* 22, 21 - 24